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ASTHMA, ANXIETY AND DEPRESSION IN PREGNANCY - THE IMPACT ON PREGNANCY, DELIVERY AND PERINATAL OUTCOMES

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Asthma, anxiety and depression in pregnancy – the impact on pregnancy, delivery and perinatal outcomes

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To Ines, Lovis and Julian

ABSTRACT

Asthma and mood disorders such as anxiety or depression are associated with adverse pregnancy, delivery, and perinatal outcomes. There is an association between mood disorders and asthma and there may be common mechanisms on how the conditions affect pregnancy outcomes. For example, some of the associations may be explained by genetic or environmental factors, familial confounding. In this thesis we have investigated how asthma and anxiety or depression complicates pregnancy and delivery outcomes in a combination of large population-based registers and smaller clinical cohorts, using family design methods to adjust for possible shared genetic and environmental factors.

In **Study I and II** we studied the associations between maternal asthma and adverse pregnancy outcomes, such as preeclampsia, placental abruption, mode of delivery, birth weight, and gestational age, using Swedish population-based cohorts. For **Study II** we identified cousins and siblings who were pregnant and gave birth during the same study period. We found that maternal asthma was associated with many of the adverse outcomes, such as preeclampsia (**Study I, II**), and that the associations were not confounded by factors shared within families (**Study II**). There were also increased risks for some adverse outcomes based on asthma severity and control (**Study I**).

For **Study III** we investigated the impact of maternal asthma on early foetal growth, assessed by routine ultrasound scan in second trimester. The study population originated from the MAESTRO study of 1693 women prospectively followed during pregnancy. We did not find any significant effect of maternal asthma on early foetal growth. There was also no difference between women with and without asthma for birth weight and gestational age

In **Study IV**, we estimated the association between maternal anxiety or depression and pregnancy outcomes using a population-based cohort. We found that maternal anxiety or depression was associated with several adverse pregnancy outcomes and that the associations were not confounded by familial factors shared by cousins and siblings. There was no interaction between asthma and anxiety or depression for any of the outcomes except for elective caesarean section. There were also higher odds for elective caesarean section in women with anxiety or depression diagnosis without medication compared to those with medication.

In conclusion, maternal asthma as well as maternal anxiety or depression were associated with several serious pregnancy complications and adverse perinatal outcomes. Familial confounding did not explain the observed associations. Apart from elective caesarean section, we did not see any interaction between maternal asthma and anxiety or depression on the studied adverse pregnancy outcomes. This means that targeting the asthma disease as well as anxiety/depression in the pregnant woman will continue to be important in reducing risks for adverse outcomes in pregnancy. Greater awareness and proper management would most likely improve outcomes.

LIST OF SCIENTIFIC PAPERS

- I. **Rejnö G**, Lundholm C, Gong T, Larsson K, Saltvedt S, Almqvist C. Asthma During Pregnancy in a Population-Based Study – Pregnancy Complications and Adverse Perinatal Outcomes. *PLoS One*. 2014; 9:e104755.
- II. **Rejnö G**, Lundholm C, Larsson K, Larsson H, Lichtenstein P, D’Onofrio BM, Saltvedt S, Almqvist C. Adverse Pregnancy Outcomes in Asthmatic Women: A Population-Based Family Design Study. *Journal of Allergy and Clinical Immunology: In Practice*. 2017 Sep 20. pii: S2213-2198(17)30561-5.
- III. **Rejnö G**, Lundholm C, Saltvedt S, Larsson K, Almqvist C. Maternal Asthma and Foetal Growth, the MAESTRO Study. (*Manuscript*)
- IV. **Rejnö G**, Lundholm C, Öberg S, Lichtenstein P, Larsson H, D’Onofrio BM, Larsson K, Saltvedt S, Brew BK, Almqvist C. Association Between Maternal Anxiety, Depression and Asthma and Adverse Pregnancy Outcomes – A Population Based Study. (*Submitted for publication*)

RELATED PUBLICATIONS

(not included in thesis)

- I. Almqvist C, **Rejnö G**. Birth mode of delivery in the modern delivery ward - indication improves understanding of childhood asthma. *Clinical & Experimental Allergy*. 2013 Mar;43(3):264-7
- II. Gong T, Lundholm C, **Rejnö G**, Mood C, Långström N, Almqvist C. Parental socioeconomic status, childhood asthma and medication use--a population-based study. *PLoS One*. 2014 Sep 4;9(9):e106579.

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LIST OF ABBREVIATIONS

ACT	The Asthma Control Test
ATC	Anatomical Therapeutic Chemical Classification
β_2	Beta-2 adrenergic receptor
BMI	Body Mass Index
BPD	Bi-parietal diameter
BW	Birth Weight
CES-D	The Centre for Epidemiologic Studies Depression Scale
CI	Confidence Interval
CRL	Crown-Rump Length
CS	Caesarean Section
DAG	Directed Acyclic Graph
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
FeNO	Fraction of Exhaled Nitric Oxide
FEV ₁	Forced Expiratory Volume in One Second
FL	Femur Length
FVC	Forced Vital Capacity
GA	Gestational Age
GINA	The Global Initiative for Asthma
ICD	International Classification of Diseases
ICS	Inhaled corticosteroid
IgE	Immunoglobulin E
LABA	Long acting β_2 -agonist
LISA	Longitudinal Integration Database for Health and Labour Market Studies (Longitudinell integrationsdatabas för Sjukförsäkrings- och Arbetsmarknadsstudier)
LTRA	Leukotriene Receptor Antagonist
MAESTRO	Maternal Asthma Events, Stress and Offspring
MBR	The Swedish Medical Birth Register
MGR	The Swedish Multi Generation Registry

NPR	The Swedish National Patient Register
OR	Odds Ratio
PANAS	The Positive and Negative Affect Schedule
PDR	The Swedish Prescribed Drugs Register
PEF	Peak Expiratory Flow
PSS	The Perceived Stress Scale
RCT	Randomised Controlled Trial
RERI	Relative Excess Risk due to Interaction
SABA	Short acting β_2 -agonist
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor

1 INTRODUCTION

A pregnancy can be demanding on the pregnant woman and, although in many cases uneventful, sometimes associated with several adverse outcomes such as preeclampsia, instrumental delivery, premature birth, and low birth weight of the child.

Having a chronic disease while pregnant is also associated with adverse outcomes and although continued medication is generally recommended, many pregnant women are under-medicated. Among the most common chronic diseases in all age-groups is asthma, which has the potential to complicate the course of pregnancy. Asthma is also associated with anxiety and depression, which in turn may also affect pregnancy.

The overall aim for the thesis is to study the association between asthma, anxiety or depression and pregnancy, delivery, and perinatal outcomes, using advanced family design in population-based national registers and a clinical cohort.

2 BACKGROUND

2.1 ASTHMA

2.1.1 Asthma prevalence and characteristics

Asthma is one of the most common chronic diseases affecting more than 300 million people worldwide¹ with a prevalence in some countries of up to 20%.² In Sweden, the prevalence is estimated to 8-10% in adults.^{3,4} It can present itself in various ways but is commonly characterised by chronic inflammation and obstructive airways. Usually, to diagnose asthma, a history of respiratory symptoms is needed. Symptoms include wheezing, chest tightness, cough, and shortness of breath in combination with reduced expiratory air flow. Even without treatment, asthma can produce mild symptoms and vary over time, especially if associated with allergic respiratory disease such as pollen allergy, or in some cases respiratory tract infections such as the common cold.⁵ There are also episodes of more severe symptoms with even life-threatening complications (exacerbations) which pose significant burden on the bearers of disease as well as health care systems.⁶

There is diversity in asthma and there are several different phenotypes described which include both allergic- and non-allergic asthma as well as late-onset asthma.⁷ There is, however, poor correlation between the specifics of different phenotypes and treatment responses.⁸

2.1.2 Asthma diagnosis and treatment

According to Global Initiative for Asthma (GINA) guidelines⁵, asthma diagnose is based on criteria such as a history of more than one of the symptoms wheeze, shortness of breath, cough, and chest tightness which vary over time and often are triggered by a stimulant (such as cold air, exercise).

To obtain an adequate asthma control, it is necessary to continuously evaluate symptoms. For this purpose, in adults as well as in adolescents and children, some asthma control tools are available and widely used, such as the Asthma Control Test (ACT), in which a score is set based on different levels of symptoms.^{9,10} However, only evaluating current symptoms might lead to inadequate treatment since respiratory symptoms can be due to other conditions than asthma (obesity, lack of fitness etc.) and some patients also have few symptoms despite a low lung function.

Spirometry is an essential instrument in evaluating asthma status and control. It should be done in a standardised way with highly trained staff. If a reversibility test is to be done, which is often the case to discern chronic obstructive disease from reversible disease (asthma), the participant (patient) needs to be on medication hiatus at least for 4 hours before the examination if the participant is using short acting β_2 -agonists. Long acting β_2 -agonists should be avoided for at least 12 hours and smoking at least one hour prior to testing. Results are associated with patient's age, gender, height, and weight and to properly interpret the

findings these variables need to be taken into consideration. The participant is first asked to do a forced expiratory manoeuvre, which will be repeated to get information on the FEV₁ (forced expiratory volume in one second). To test for reversibility, the participant is then asked to inhale a short acting bronchodilator – for instance salbutamol or terbutaline, and then do the test all over again.^{11, 12} If obstructive airways are present, the participant should perform better after medication, resulting in an improved FEV₁,¹³ Figure 1.

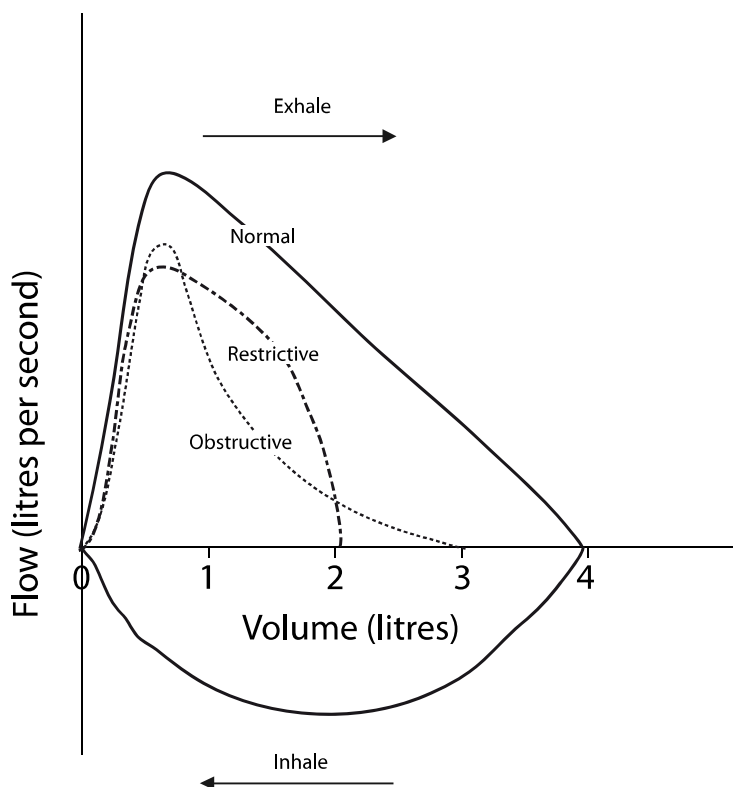


Figure 1. Results of spirometry showing a normal (triangle-shaped) curve, a restrictive curve, and an obstructive curve. The forced vital capacity (FVC) is the amount of air (in litres) forcibly expired after maximum inhalation. Forced expiratory volume in one second (FEV₁) is the volume (litres) forcibly expired in the first second after maximum inhalation.

Just as lung function tests can add to the clinical picture¹⁴, exhaled nitric oxide (NO), a marker of airway inflammation, can together with data on FEV₁ and FEV₁/FVC predict risk of exacerbations.¹⁵⁻¹⁷

Asthma treatment is handled in a step-wise approach.⁵ In step 1, a short-acting symptom reliever is used, often a short-acting β_2 -agonist (SABA). If this is not enough, medication with an inhaled corticosteroid (ICS) taken regularly is initiated, sometimes with addition of leukotriene receptor antagonists or low dose theophylline (step 2). A short-term PEF (Peak Expiratory Flow) monitoring can be used to evaluate the response to treatment.

If the asthma is moderate to severe (step 3-4) addition of long acting β_2 -agonists (LABA) and increasing doses of ICS is needed. A more severe asthma that does not respond to inhalation treatment (step 5) may require add-on treatment such as anti-IgE and oral corticosteroids (Figure 2).

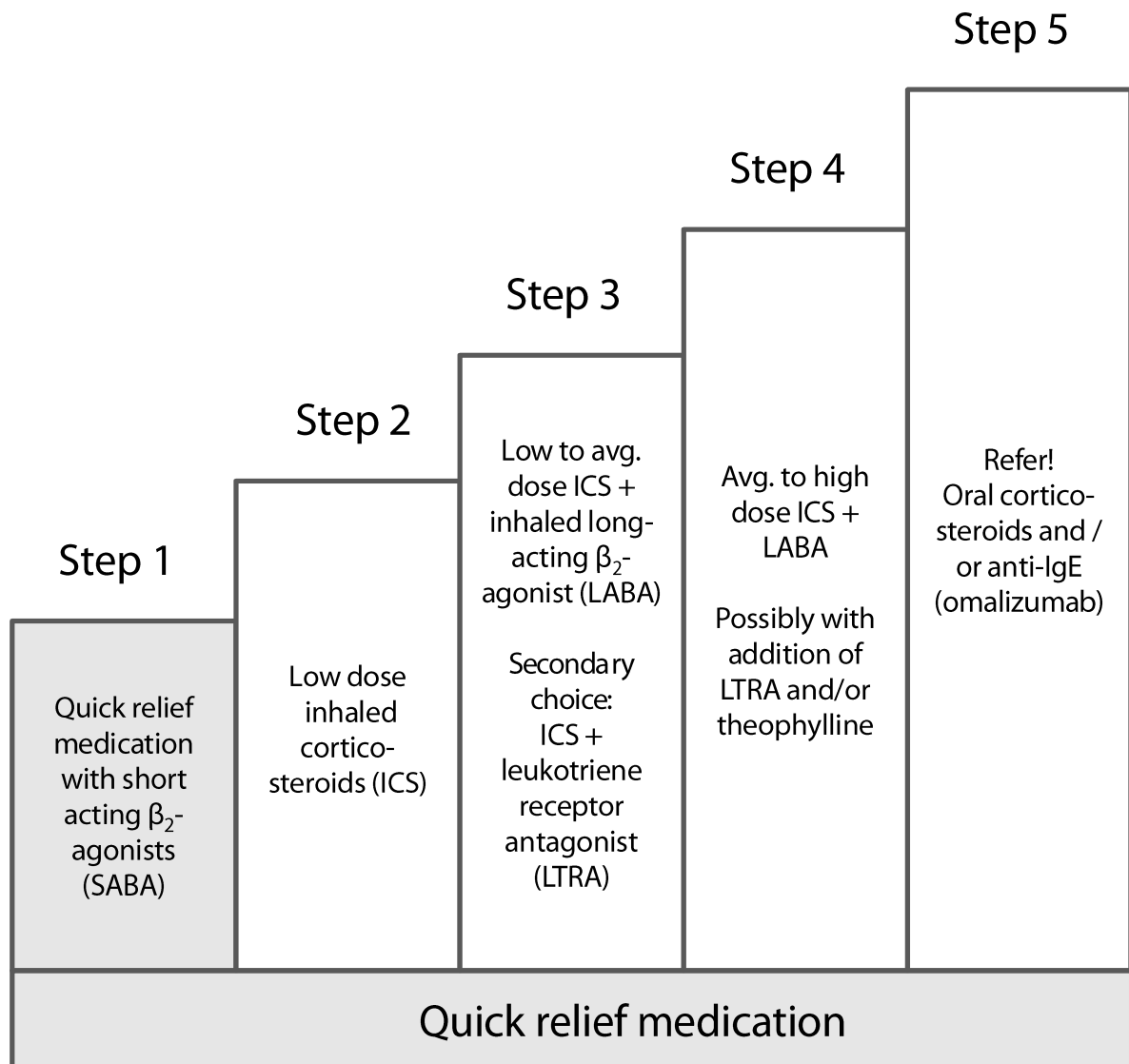


Figure 2. Step-wise approach of asthma treatment.⁵

2.1.3 Asthma and pregnancy

Asthma is one of the most common chronic diseases during pregnancy.^{18, 19} Asthma symptoms may increase during pregnancy, which can be attributable either to worsening of asthma due to the pregnancy itself or inadequate medication.^{20, 21}

Mild and moderate well-controlled asthma is generally associated with an uncomplicated course of both pregnancy and delivery, but maternal asthma has also been associated with an increased risk for pregnancy complications, adverse labour characteristics, and perinatal

outcomes²²⁻³² and poor asthma control seems to increase the risk of preeclampsia, preterm delivery and small for gestational age.^{33, 34} Moreover, exacerbations of asthma during pregnancy, often triggered by non-adherence to inhaled corticosteroid medication, are associated with risk of a low birth weight in offspring.³⁵

Although there are several studies on the association between asthma in pregnant women and pregnancy outcomes,^{22, 23, 25, 30, 36, 37} the previous studies are non-consistent.^{19, 24, 27, 38-40} It has been suggested that this discrepancy might be caused by variation in study size and that participation in smaller prospective studies is associated with better disease control and therefore better outcomes.⁴⁰ Thus, there is a call for larger studies to assess the effect of maternal asthma, severity and control on pregnancy complications, labour, and perinatal outcomes. Larger studies may also allow adjustment for confounding factors that may affect exposure and outcomes, such as socioeconomic status, maternal weight and shared genetics and common environment.

2.2 ANXIETY AND DEPRESSION

2.2.1 Prevalence and characteristics of anxiety and depression

Mood disorders such as anxiety and depression are common in all populations and it is estimated that about 20-30% will be affected some time during their lifetime.^{41, 42} Anxiety and depression are closely associated conditions, overlapping to a high extent for instance in terms of medication. They may affect not only psychological well-being but also other diseases such as asthma.^{43, 44}

Stress is considered a possible inductor of anxiety and depressive-like symptoms⁴⁵ and anxiety and depression are often referred to as psychological distress where stress perhaps is situated in one end of a spectrum.⁴⁶⁻⁵⁰ Stress to some extent is very common and probably not dangerous, but too much stress might cause clinical symptoms like anxiety or depression, and ultimately lead to physical conditions such as adverse outcomes in pregnancy and maybe later morbidity in the child.⁵¹ Major stress events such as bereavement⁵² can be measured in registers but other types of stress are more difficult to assess. Using validated questionnaires⁵³ is a common approach, however they require clinical cohorts which are smaller and have lower power.

2.2.2 Diagnosis and treatment of anxiety and depression

Anxiety and depression are diagnosed by means of specific criteria, and widely used instruments are the DSM (Diagnostic and Statistical Manual of Mental Disorders)⁵⁴, and ICD (International Classification of Disease).⁵⁵ The instruments have differences, but the overall concordance is often good.⁵⁶ Different scales are used as a complement and evaluation of treatment of mood disorders, such as Centre for Epidemiologic Studies Depression (CES-D),⁵⁷ the Positive and Negative Affect Schedule (PANAS)⁵⁸ and the Perceived Stress Scale (PSS).⁵⁹

Antidepressant medication is very common and, in the USA, used by on average 15% of women in reproductive age.⁶⁰ During pregnancy the figures are lower and a recent Nordic study by Zoega et al. showed an exposure to antidepressant drugs during pregnancy of about 4%.⁶¹ The basis of pharmacological treatment is a selective serotonin reuptake inhibitor (SSRI) – although the use of serotonin-norepinephrine reuptake inhibitors (SNRI) have increasingly become an alternative,⁶² often in combination with a mild sedative for improvement of sleep and anxiety relief.⁶³

2.2.3 Anxiety, depression, and pregnancy

During pregnancy, anxiety and depressive symptoms are at least as common as in non-pregnant women with a prevalence of 6-15%.⁶⁴⁻⁶⁶ Similar to asthma being a risk factor for adverse pregnancy and delivery outcomes, women reporting anxiety and depression during pregnancy have been displaying increased odds ratios for several of the same adverse outcomes.⁶⁷⁻⁷² The mechanisms for the associations between anxiety or depression and adverse pregnancy outcomes are yet to be elucidated and factors shared within families (such as common genes and common environment) may play a role.⁷³

An association between anxiety, depression and asthma has been shown previously⁷⁴ and may have common mechanisms for adverse pregnancy outcomes.⁶⁷⁻⁶⁹ Why this similarity exists and the mechanism behind it is however not fully clarified, and socioeconomic factors may have a large impact as well as common immune processes.^{74, 75} There may be interaction between maternal asthma and maternal anxiety or depression that leads to increased risks of adverse outcomes above what would be expected from the risk of each condition combined.

2.3 PREGNANCY AND ADVERSE OUTCOMES

2.3.1 Pregnancy Characteristics

Pregnancy is a state of induced immuno-suppression⁷⁶ which leads to inhibition of immune responses. This is a necessary process because of the foreign antigens presented by the foetus.⁷⁷ During pregnancy, with the enlarging uterus, the diaphragm is elevated up to 4 cm which leads to a reduced functional residual capacity (the amount of air left after passive expiration). In a normal pregnancy, there are no significant alterations in forced vital capacity, peak expiratory flow rate or forced expiratory volume in 1 second.⁷⁸

2.3.2 Pregnancy Complications

Although most pregnancies are uneventful in terms of complications there are adverse outcomes in pregnancy and delivery that can affect the woman, foetus, or both.

Preeclampsia during pregnancy affects 3-7% of all pregnant women and is a potentially life-threatening complication characterized by hypertension, elevated liver enzymes, proteinuria, headaches, and intrauterine growth restriction. The disease may be manifested after gestational week 20 and there is no real treatment except delivery.⁷⁹ There are several hypotheses as to the pathogenesis of the disease. One of the most commonly accepted is a

two-step model with, firstly, a defect in the placental formation,⁸⁰ perhaps due to an immunological maladaptation. The weakened utero-placental blood flow causes an impaired oxygen transport resulting in free radicals, an oxidative stress and eventually permanent tissue damage. In a second step, leakage of particles from the foetus due to the tissue damage leads to general endothelial damage and a systemic inflammation.⁸¹

Gestational diabetes is a condition that affects 6% of all pregnancies and is associated with other pregnancy complications such as preeclampsia, caesarean section, foetal macrosomia, shoulder dystocia, and neonatal hypoglycaemia.⁸²

Premature contractions and premature rupture of membranes are associated with premature delivery which is a major contributor to perinatal morbidity and mortality.⁸³

A rare, but serious condition is **placental abruption** in which the placenta in part or in whole detaches prior to delivery. It is associated with severe morbidity and mortality in both mother and foetus/child⁸⁴ and previous studies have shown an association between maternal asthma during pregnancy and placental abruption.⁸⁵

Labour dystocia is a risk factor for interventions during labour and is the most common indication for primary caesarean sections. Factors that contribute to prolonged labour and labour dystocia include advanced maternal age, obesity and labour induction.⁸⁶

The **mode of delivery** is associated with outcomes for mother and child – both in long term and short perspective. Although sometimes life-saving, caesarean section is also associated with both foetal and maternal morbidity.⁸⁷

Haemorrhage after delivery is the leading cause of maternal mortality worldwide. It is usually caused by uterine atony, lacerations, retained placenta, placenta accreta, coagulation defects, or uterine inversion but can also be caused by infections and genetic coagulation defects, such as von Willebrand's disease.⁸⁸

Foetal growth can be affected by many conditions including and maternal asthma.^{89, 90} It is unclear if this occurs early in pregnancy or later. Foetal age is routinely determined by a second trimester ultrasound scan, in gestational week 18-20, but can be measured earlier. In the first trimester, gestational age by ultrasound scan is calculated by measurement of the crown-rump-length (CRL) and bi-parietal diameter (BPD).^{91, 92} Second trimester ultrasound scan estimates the gestational age by measuring the femur length (FL) and the BPD,⁹³⁻⁹⁵ and later during pregnancy repeated scans can assess intrauterine foetal growth.⁹⁶

The **Apgar score** was developed in 1952 by Dr. Virginia Apgar as a method for assessing the neonate's immediate response to resuscitation at 1, 5, and 10 minutes after birth. The score is widely used but should not be interpreted as evidence of **asphyxia** in the child.⁹⁷

2.4 EPIDEMIOLOGICAL INVESTIGATION OF OBSERVED ASSOCIATIONS

2.4.1 Epidemiological methods

To study the association between asthma and stress/anxiety/depression on the one hand and pregnancy, delivery, and perinatal outcomes on the other, one must rely on epidemiological approaches, of which some are described below.

2.4.1.1 *Randomised Controlled Trial*

The gold standard of evaluating a certain treatment or intervention is a randomised controlled trial (RCT) where a population is divided into randomly selected groups. One group receives an intervention whereas the other group receives no intervention in such a manner that neither participants nor testers are aware of what group they are in. A perfectly executed RCT can both show associations and state if there is causality, e.g. a given medication treats a certain disease.

RCT:s, however are difficult, costly and in many cases not possible to conduct. Also, if there is no intervention to be studied other approaches are needed.

2.4.1.2 *Observational cohort study*

A cohort study is an analytical observational study where one or several outcomes are measured in a group of individuals that are either exposed or unexposed to a certain variable and followed up after a specified time. The cohort can be patients selected based on medical records, a clinical cohort of prospectively collected data, register based data or a combination thereof. In Sweden, the universal use of the personal identity number, which is a unique identifier for each resident, enables linkage between different data sources.⁹⁸ There are several Swedish national registers held by the National Board of Health and Welfare that can be used when studying disease.

When doing an epidemiological study of pregnant women, the usage of the Medical Birth Register (MBR) is a very efficient path to take if one wants to create a large cohort. Linkage with other registers enables addition of data such as prescribed drugs, diagnoses and socioeconomy. A large dataset with many observations and many co-factors also allows for adjustment in calculations for potential confounders that might otherwise lead to a confounded, weaker or stronger association.

2.4.1.3 *Family design*

All confounders are however not known, or even measurable. For instance, there can be familial factors (genetic or common environment) that are closely associated to both exposure and outcome. With large enough number of observations, some of those unmeasured familial factors can be adjusted for by using a family-design approach.^{99, 100} In terms of family design, sibling comparison is one of the strongest. It can rule out alternative mechanisms that confound associations between early risk factors and later disease, including all unmeasured genetic and early life environmental factors shared by siblings. If an association remains after

having compared cases to unexposed siblings and cousins there is an indication that the exposure studied is a potential risk factor for the outcome. If however, an observed risk for adverse outcomes diminishes when using sibling and cousin controls, familial factor may be considered to have confounded an association observed in comparison to unrelated controls.^{101, 102} By using a family-based design, one does not confirm causality, but the method provides stronger support for a causal effect compared to ordinary observational studies.¹⁰³

2.4.1.4 Clinical cohort

Creating a clinical cohort by prospectively collecting data is more time-consuming and less efficient than a register linkage, although a clinical cohort has some important advantages over register data. For instance, all information of interest may not be available in the registers, such as bio samples and lung function measurements. Moreover, the data in the registers can be less detailed than wanted, for example asthma diagnosis is available from the registers but not results from lung function test.

3 KNOWLEDGE GAPS AND AIMS

More knowledge about the effects of asthma and asthma severity and -control is needed to identify measures to optimise care of pregnant women with asthma. This can be achieved with a combination of a register-based linkage study and a clinical cohort (**aims 1, 2 and 3**).

It is not clear if the association between maternal asthma and adverse pregnancy outcomes is causal or confounded by genetic effects or/and environmental factors. More knowledge on the effects of genes and environment on asthma during pregnancy is needed (**aim 2**).

Although studies on maternal asthma and pregnancy outcomes can be conducted using register data, more detailed and reliable data on those exposures (asthma prevalence, severity, and control) and outcomes (foetal growth in utero and pregnancy outcomes) can be collected using a clinical cohort. Also, few studies have assessed the effect of maternal asthma on ultrasound measured foetal growth⁹⁰ (**aim 3**).

Like asthma being a risk factor for adverse pregnancy and delivery outcomes, women reporting anxiety and depression during pregnancy have been displaying increased odds ratios for several of the same adverse outcomes.⁶⁷⁻⁶⁹ It is not clear whether this higher prevalence of adverse pregnancy outcomes after anxiety or depression remains after adjusting for genetic and shared environmental factors as can be done using sibling and cousin analyses. It is also not clear if there is an interaction between maternal asthma and anxiety/depression that affects adverse outcomes more than to be expected from each condition combined (**aim 4**).

The specific aims are:

- Study I. To assess possible associations between maternal asthma, pregnancy, labour, and adverse birth characteristics as well as the effects of asthma severity and control on pregnancy complications and perinatal outcomes.
- Study II. To examine, in a family design approach, whether the associations between maternal asthma and adverse pregnancy, labour and perinatal outcomes are confounded by familial factors (genes and/or environment).
- Study III. To examine, in a clinical study, how maternal asthma and asthma control affects early foetal growth and pregnancy outcomes, taking maternal background factors and confounders into account.
- Study IV. To explore whether anxiety or depression during pregnancy is a risk factor for adverse pregnancy outcomes, adjusting for familial confounding in a sibling-cousin design, and whether there is an interaction between maternal asthma and anxiety or depression.

4 METHODOLOGICAL CONSIDERATIONS

4.1 DATA SOURCES

4.1.1 Register Data

In Study I, II and IV, data were retrieved from the three registers held by The National Board of Health and Welfare (Socialstyrelsen), a government agency in Sweden under the Ministry of Health and Social Affairs, and two registers held by Statistics Sweden, a government agency responsible for official statistics and for other government statistics.

We used health registers from the National Board of Health and Welfare. **The Swedish Medical Birth Register (MBR)** is a national register that, since 1973, includes approximately 99% of all pregnancies that result in delivery. The register comprises of six main parts: 1) patient ID (mother and child), 2) social background factors, 3) mother's medical history, 4) pregnancy data, 5) delivery data and 6) perinatal data on the new born child.^{104, 105} All data in the register are prospectively collected: background factors at the first antenatal visit; data on medication use, mother's weight, tobacco use updated throughout the pregnancy; and data on pregnancy- and delivery outcomes as well as perinatal data such as foetal weight, length, and asphyxia or hypoxia, at delivery.

The National Patient Register (NPR), started in 1987, contains all diagnoses and procedures of in-patient care and, since 2001, also includes specialist out-patient care, covered to 75%.¹⁰⁶

One of the newer national registers is **the Swedish Prescribed Drugs Register (SPDR)**, which started on 1 July 2005. It contains individually based data on dispensed prescribed drugs (ATC-codes), dosage, size of package and amount, date of prescription.¹⁰⁷

From Statistics Sweden we have used **the Longitudinal Integration Database of Health Insurance and Labour Market Studies (LISA by Swedish acronym)** to study socioeconomic status such as education level and yearly income,¹⁰⁸ and **the Multi Generation Registry (MGR)** which contains information on all persons who have been registered in Sweden at some point since 1961 and born 1932 or later. The register contains connections between index persons and biological and adoptive parents.^{109, 110}

The Medical Birth Register allowed us to identify all women that gave birth during the study periods, which for Study I consisted of all Swedish women being pregnant and giving birth between 1 July 2006 and 31 December 2009 (N=284,214); for Study II and IV between 1 January 2001 and 31 December 2013 (N=1,075,153).

In Study II and IV we also identified the women's full sisters and first cousins who gave birth during the same study period using the Multi Generation Register.

4.1.2 Clinical Data

The MAESTRO cohort (Maternal Asthma Events, Stress and Offspring) was initiated in 2011. The main research questions were about the effects of maternal asthma and maternal stress on pregnancy and pregnancy outcomes. In contrast to studies based solely on register data, the MAESTRO cohort includes biological data, data from questionnaires, data on lung function measurements as well as information from patient charts and national registers.

All women that were admitted to the antenatal clinic in the first trimester of pregnancy were asked to participate, regardless of asthma or stress status. After consenting to the study, the midwife took a blood sample for IgE and DNA analyses. The participating woman then answered an online questionnaire on background factors, asthma status, stress etc. The participant also took two saliva samples (morning and evening sample) and sent them to a biobank. The same questionnaires and saliva samples were also taken in weeks 28-32 of pregnancy and 6 months after delivery. Around 250 women, half of which stated asthma or asthma-like symptoms in the first questionnaire and the other half healthy controls, were additionally asked to participate in spirometry tests. These included a reversibility test and provided data on FeNO and FEV₁, in weeks 28-32 and 6 months after delivery. The lung function measurements were conducted at Karolinska Institutet, the Department of Medical Epidemiology and Biostatistics. Data regarding pregnancy and birth outcomes, as well as ultrasound records, with data on gestational age and foetal growth was collected from the antenatal clinic and delivery ward medical records. Additional data on diagnoses and dispensed medication were collected from the National Patient Register and the Swedish Prescribed Drugs Register. A flow chart of the study design is shown in Figure 3.

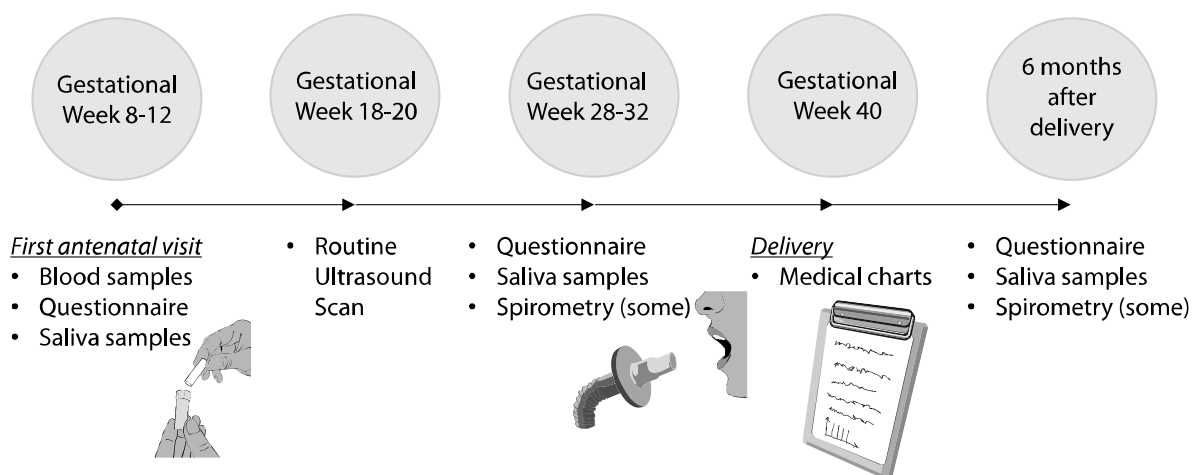


Figure 3. Timeline of the MAESTRO study. Questionnaire and saliva sampling conducted at home. Blood sampling and lung function testing conducted at clinic. All available medical records and ultrasound data were collected after birth.

4.2 EXPOSURES

4.2.1 Register Data

Study I and II had maternal asthma as the exposure, in Study I asthma severity and asthma control were also assessed.

An asthma ever diagnosis was identified if data on asthma disease was present in any of three different registers. Firstly, the Medical Birth Register as a tick box for asthma/lung disease ever- a question put by the treating midwife at the first antenatal visit in the first trimester of the pregnancy. Secondly, we identified physician diagnosis of asthma the National Patient Register, by the means of code 493 according to International Classification of Diseases, Ninth Revision (ICD-9), and codes J45 and J46 according to the International Classification of Diseases, Tenth Revision (ICD-10). For Study I, the diagnosis was identified in the year before pregnancy or during pregnancy (a current asthma diagnosis) and in Study II we used asthma diagnosis ever from the age 15 until delivery. Thirdly, in the Swedish Prescribed Drug Register we defined asthma as women with asthma medication (Anatomical Therapeutic Chemical Classification, ATC, codes R03AC, R03AK, R03BA, R03DC, H02) dispensed at least twice in the year before pregnancy and until delivery. The use of register-based data when assessing asthma disease has been previously validated.¹¹¹ Figure 4 shows the overlap in asthma disease between the different registers used. The majority of information came from the Medical Birth Register, and The National Patient Register mostly overlaps with the other registers but was still important in identifying 1% of the asthma cases.

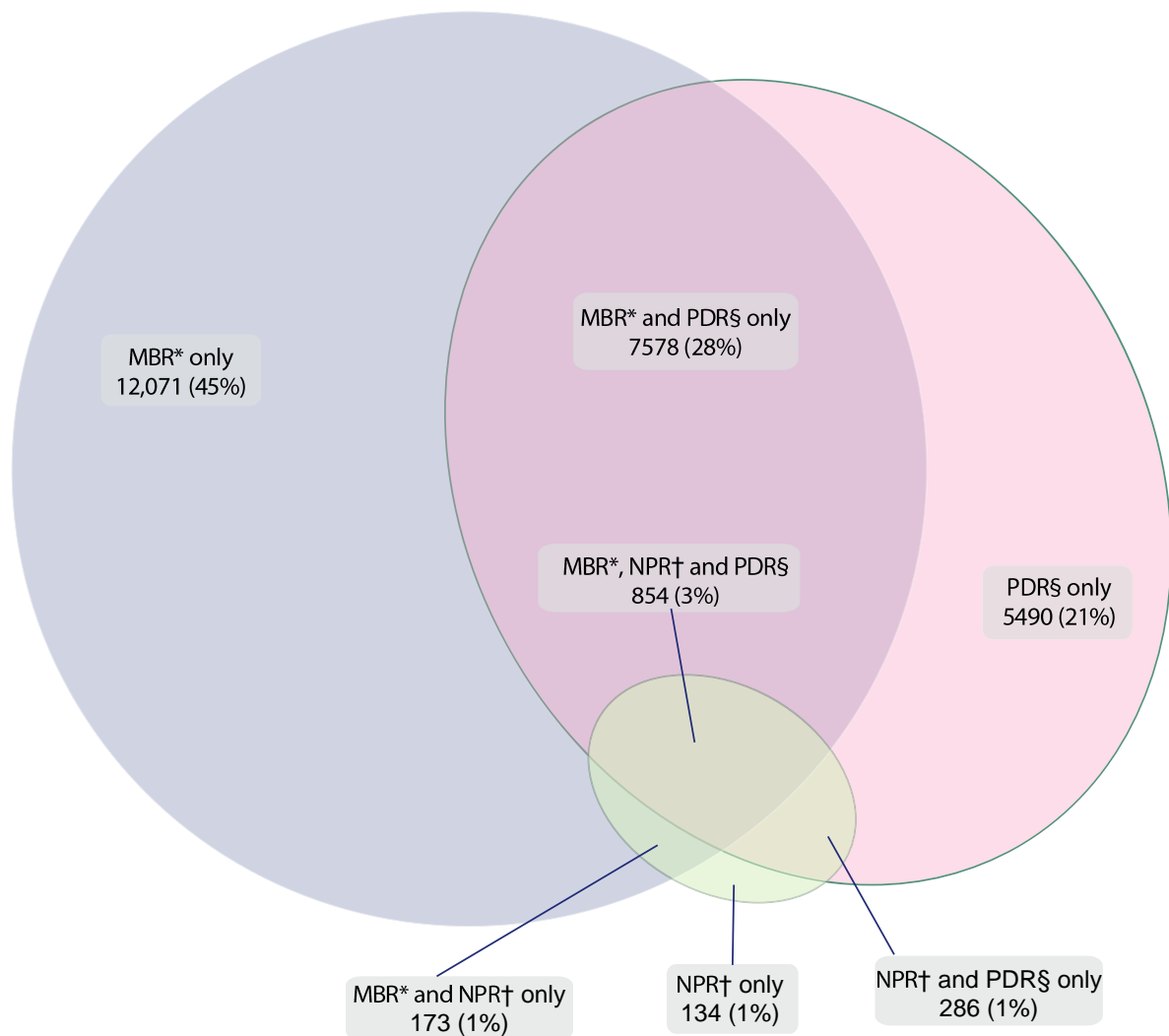


Figure 4. The overlap of asthma ever in the different registers used for Study I.
**The Medical Birth Register, §The Prescribed Drugs Register, † The National Patient Register.*

Asthma severity and asthma control was assessed in Study I using a previously validated index based on Canadian data by Firoozi et al.¹¹² By looking at average prescribed doses of asthma medication as well as diagnosis for hospitalisation or emergency visits for asthma it is possible to determine both severity and control. The index was slightly modified by changing the number of filled prescriptions for long-acting β_2 agonists, theophylline, and leukotriene receptor antagonists from six to two over a period of 12 months in order to adhere to Swedish prescription patterns, Table 1.

Table 1. Asthma severity modified from Firoozi et al.¹¹²

Asthma severity and control		Inhaled corticosteroids (ICS), daily dose, µg (daily dose of ICS in beclomethasone-chlorofluorocarbon equivalent over a 12-month period)	Other controller therapy (at least two prescriptions or long-acting β ₂ agonists (LABA), theophylline or leukotriene receptor antagonists (LTRA) dispensed over a 12-month period)	Short acting β ₂ agonists (SABA) doses per week (average doses inhaled SABA per week calculated over a 12-month period)	Marker of moderate to severe exacerbations (an emergency department visit for asthma, a hospital admission for asthma or a filled prescription of an oral corticosteroid over a 12-month period)
Mild asthma					
	Controlled	0-500	No	0-3	No
		0-250	Yes	0-3	No
	Uncontrolled	0-250	Yes	0-3	Yes
		0-500	No	0-3	Yes
		0-250	Yes	4-10	No
		0-500	No	4-10	No
Moderate asthma					
	Controlled	251-500	Yes	0-10	No
		501-1000	Yes/No	0-10	No
		>1000	Yes/No	0-3	No
	Uncontrolled	0-250	Yes	4-10	Yes
		0-500	No	4-10	Yes
		0-250	Yes	>10	No
		0-500	No	>10	No
		251-500	Yes	>10	No
		251-500	Yes	0-10	Yes
		501-1000	Yes/No	>10	No
		501-1000	Yes/No	0-10	Yes
		Severe asthma			
	Controlled	>1000	Yes/No	4-10	No
		0-1000	Yes/No	>10	Yes
	Uncontrolled	>1000	Yes/No	0-10	Yes
		>1000	Yes/No	>10	Yes/No

For Study IV, our main exposure was current anxiety or depression and defined as at least two prescriptions of medication for anxiety or depression in the Swedish Prescribed Drugs Register (ATC-codes N05B and N06A) from the year before pregnancy until delivery and/or having an ICD-10 code for anxiety or depression (F30-34, F38-42, F44-45, F48) in the National Patient Register during the same period. Possible interaction between maternal asthma and anxiety or depression was evaluated in Study IV as well and we identified women with current asthma using data from the National Patient Register (ICD-10 codes J45 and J46) and the Prescribed Drugs Register (ATC-codes R03AC, R03AK, R03BA, and R03DC) as in Study I above.

4.2.2 Clinical Data

The exposures used in Study III of the thesis (the study based on the MAESTRO cohort) were maternal asthma ever as assessed from the medical charts (as a tick box for asthma/lung disease from the first antenatal visit), or from the first trimester questionnaires (self-reported physician diagnosed). The questionnaire also included data on asthma control from the Asthma Control Test (ACT), where a score ≤ 19 indicates uncontrolled and a score ≥ 20 indicates controlled disease.⁹

4.3 OUTCOMES

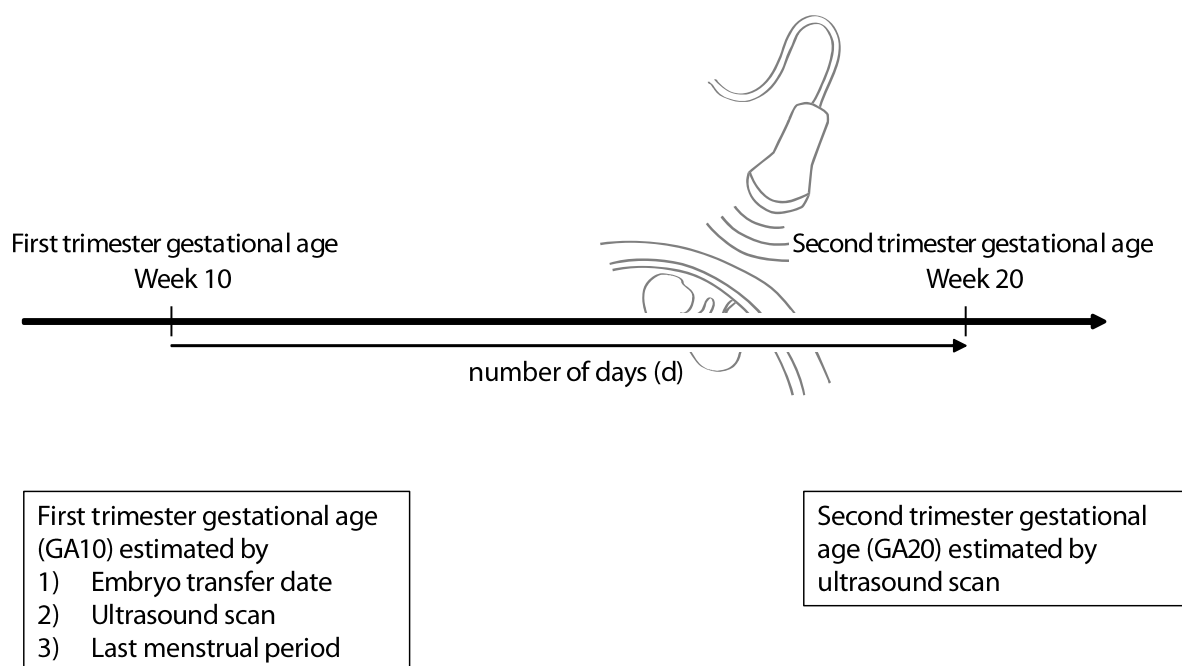
4.3.1 Register Data

Our studied outcomes in Study I were all collected from the Medical Birth Register and based on pregnancy- and delivery ICD-10-codes for preeclampsia/eclampsia (O14-15), gestational diabetes (O24), haemorrhage during pregnancy (O46), premature contractions (O47), premature rupture of membranes (O42), placental abruption (O45), dystocia during labour, induced/spontaneous onset of labour, caesarean section, CS, (which included elective or emergency CS prior to or emergency CS after onset of labour) and vaginal instrumental delivery (O62, O66.5, O81, O82). Based on the delivery codes, delivery mode was categorised as 1) vaginal, non-instrumental delivery, 2) elective CS (before start of labour), 3) vaginal instrumental delivery, and 4) emergency CS prior to or after start of labour. Birth outcomes and post-partum characteristics were also collected from the Medical Birth Register. Birth weight, gestational age, information on small and large for gestational age (defined as birth >2 standard deviations below or above reference curve for children of similar gestational age)¹¹³ were collected alongside data on Apgar score at 5 minutes,¹¹⁴ haemorrhage after delivery (O72) and asphyxia/hypoxia in the child (P20-P21).

For Study II and IV we identified the outcomes in the same way as in Study I but looked at fewer outcomes; preeclampsia/eclampsia, placental abruption, delivery mode, birth weight, gestational age as well as small and large for gestational age.

4.3.2 Clinical Data

In Study III we collected all data on the outcomes from the medical records. Our outcomes were early and late foetal growth as measured by ultrasound around week 20¹¹⁵ and birth weight. Early foetal growth was defined as growth discrepancy between first and second trimester estimates of gestational age, Figure 5.



Expected Gestational Age at Week 20 (expGA_{20}) = $[\text{GA}_{10}] + [\text{d}]$

Discrepancy at Week 20 = $[\text{GA}_{20}] - [\text{expGA}_{20}]$

Figure 5. Illustration of estimation of first and second trimester gestational age, and discrepancy between estimated and expected gestational age around gestational week 20.

In the first trimester, we calculated the gestational age from 1) embryo transfer date, 2) first trimester ultrasound closest to week 10, 3) last menstrual period as reported at first antenatal visit, if an ultrasound was not available.

The comparison between estimated and expected gestational age at the second trimester ultrasound resulted in a negative discrepancy (the foetus was smaller than expected), positive (the foetus was larger than expected) discrepancy, or no discrepancy (no deviation from expected pregnancy length).

Positive and negative discrepancy was defined as deviation in number of days below 10th percentile or above 90th percentile from expected measurement. The reference category chosen was all measurements – discrepancies or not – *between* the 10th and 90th percentiles.

We collected data on gestational age at birth, birth weight and birth length from the obstetric medical records.

4.4 COVARIATES

4.4.1 Register Data

Possible confounders were chosen for studies I, II and IV based on previous knowledge about their effects on both exposures and outcomes and by the means of directed acyclic graphs (DAG:s).¹¹⁶ DAG:s are powerful when trying to identify covariates necessary to obtain

unconfounded estimates and are very helpful in determining pathways that are otherwise difficult to imagine, Figure 6.

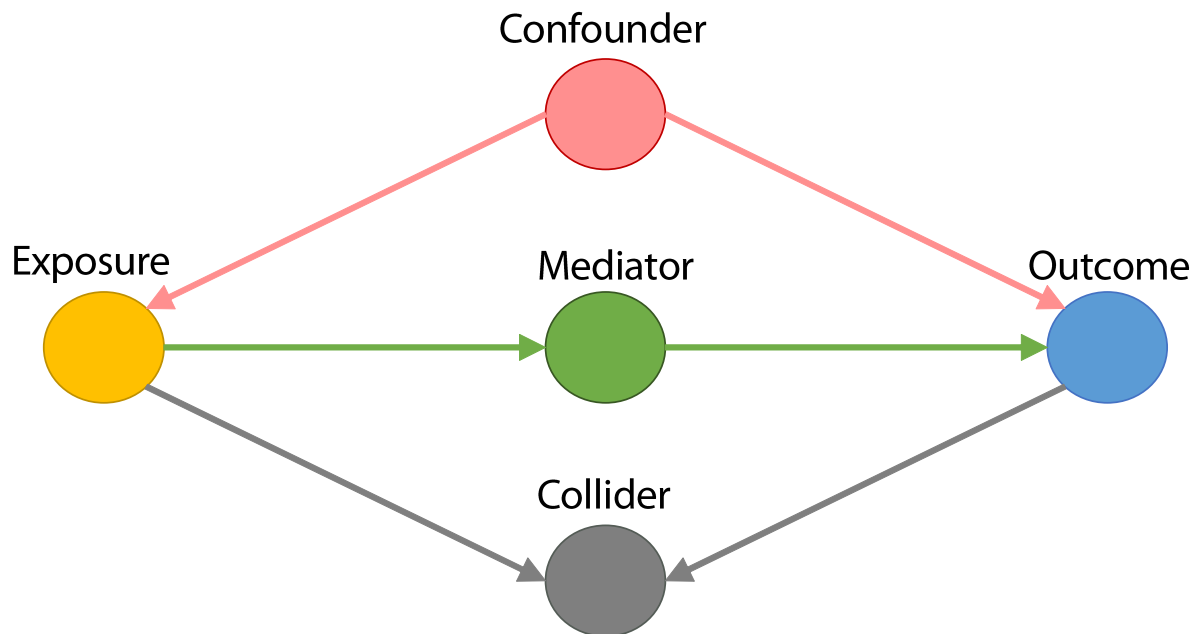


Figure 6. A DAG showing associations between exposure (yellow circle) and outcome (blue circle) with possible confounding factor, affecting both exposure and outcome (pink circle). Green line showing causal pathway. Often a mediator is present in the causal pathway (green circle). A collider (grey circle) is a factor that is caused by both exposure and outcome. Adjusting for a collider opens that path, causing a spurious association.

The covariates chosen were collected from the Medical Birth Register and the longitudinal integration database for health and labour market studies (LISA) maintained by Statistics Sweden. The covariates used in the studies were: self-reported smoking at first antenatal visit (none, 1-9 cigarettes per day, > 9 cigarettes per day); body mass index (BMI in kg/m²) at first antenatal visit and calculated by height and weight; maternal age; parity; cohabitation; country of birth (Sweden/other Scandinavian countries/rest of the world); and socioeconomic status defined as the highest attained level of education. Data on maternal age and parity were recorded at delivery.

4.4.2 Clinical Data

We adjusted for possible confounders known to be associated with both the exposure and the outcomes, as in the register-based studies. They were maternal BMI, maternal smoking at first antenatal visit, level of education and data on cohabitation. As for exposure and outcomes, all data on covariates in Study III was collected from the medical records and the questionnaires.

4.5 STATISTICS

Linear and logistic regression

In a first step we studied the prevalence of asthma (Study I, II, III, and IV) and anxiety or depression (only Study IV) and the association with chosen covariates and outcomes. We then performed logistic and linear regression analyses for categorical and continuous variables. We estimated crude and adjusted odds ratios (OR) and beta coefficients with 95% confidence intervals for the full cohort. To account for the clustering of observations within women with multiple deliveries a sandwich estimator for the standard errors was used.

In Study I, additional logistic regression analyses of asthma severity (with moderate/severe asthma compared to mild asthma as reference) and asthma control (uncontrolled asthma versus controlled) were done. The Holm-Bonferroni method¹¹⁷ was also applied to evaluate what significant results from the primary analyses would remain when applying an overall 5% significance level for those tests.

Family design

In Study II and IV we also used conditional logistic regression, conditioning on full sibling pairs (same mother and father) and cousin pairs (common grandparents) in separate analyses, and for the continuous outcomes a linear regression model with fixed effects estimator. By doing so we could estimate associations between exposures and outcomes adjusted for genetic factors (full sisters share on average 50% and first cousins share on average 12.5% of segregated genes) and shared (familial) environment. The use of conditional regression, a within-family design, allows us to determine if the statistical association seen is due to familial confounding – if the comparison of discordant cousins or siblings will result in changed estimates, with a possible gradient from the full cohort, to cousins, to siblings, a possible familial confounding is present.¹⁰⁰ As in the full cohort analyses, some women contributed with more than one pregnancy. Since there was dependency within clusters, we used bootstrapping to estimate correct 95% confidence intervals for the cousin and sibling analyses.

Testing for Effect Modification and Interaction

In Study I, we tested for effect modification of asthma control on disease severity by including interaction terms in the models. For Study IV, we also looked at the possible interaction between maternal asthma and maternal anxiety or depression by including an interaction term. In the linear regression models (with the continuous outcomes) this corresponds to interaction on the additive scale and in the logistic regression models (dichotomous outcomes) on the multiplicative scale. The differences in effects between the different models in both Study I and Study IV were tested with the likelihood ratio test.

When evaluating possible interaction between two exposures it is not sufficient to only look at interaction on the multiplicative scale, which is common if testing for interaction in logistic regression models. Although multiplicative interaction may be important when trying to

assess causal mechanisms, looking at interaction on the additive scale can help determining importance on a public health scale. We estimated additive interaction for the dichotomous outcomes by calculating Relative Excess Risk due to Interaction (RERI).¹¹⁸

5 RESULTS AND DISCUSSION

5.1 STUDY I AND II

The asthma prevalence in Study I and II in pregnant women was around 10%. In Study I (n = 284,214) we found that when the mothers had asthma there were increased risks for; preeclampsia/eclampsia, haemorrhage during pregnancy, premature contractions, premature rupture of membranes, placental abruption, labour dystocia, caesarean section, instrumental delivery, low birth weight, low gestational age, and small for gestational age, Figure 7a-b.

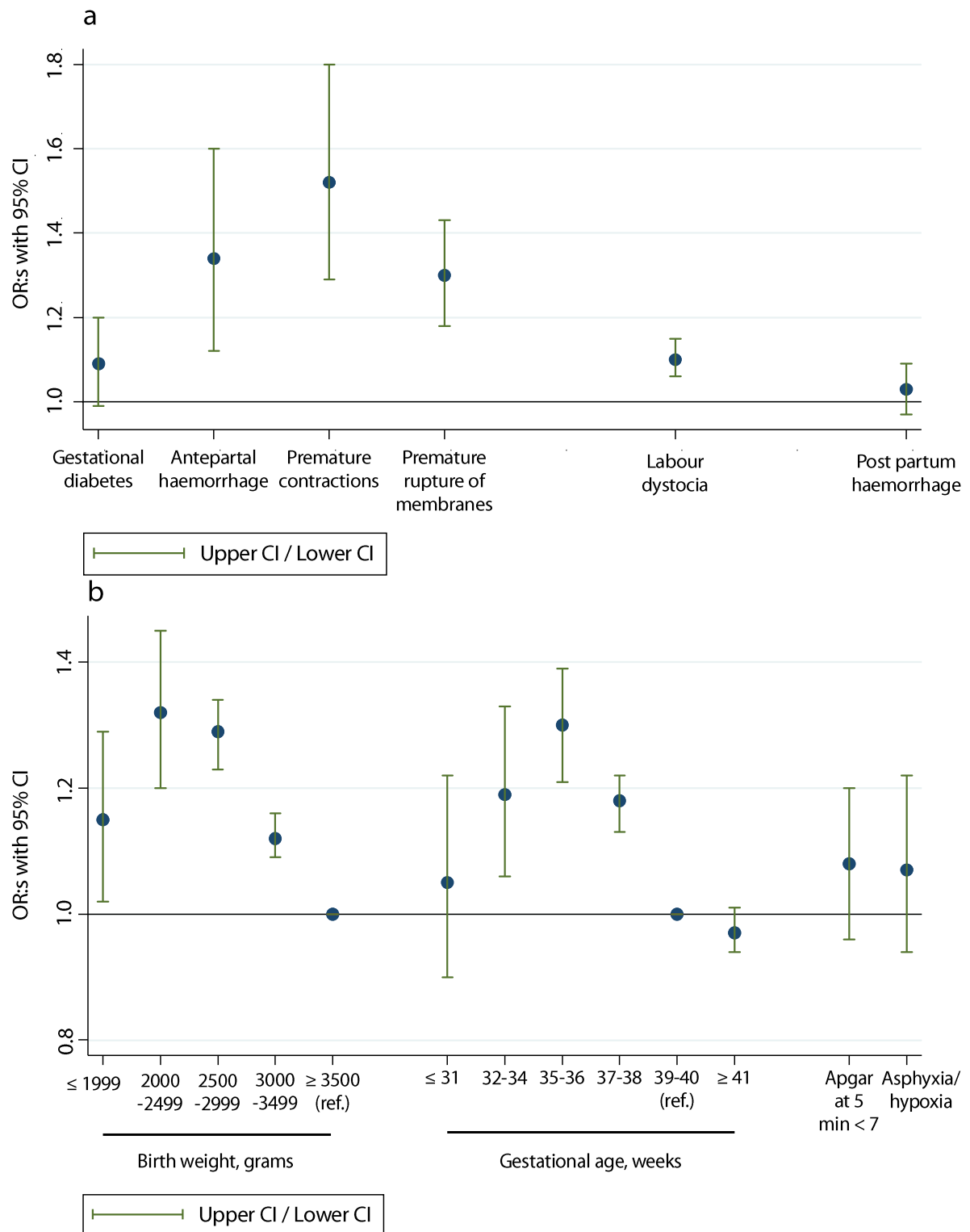
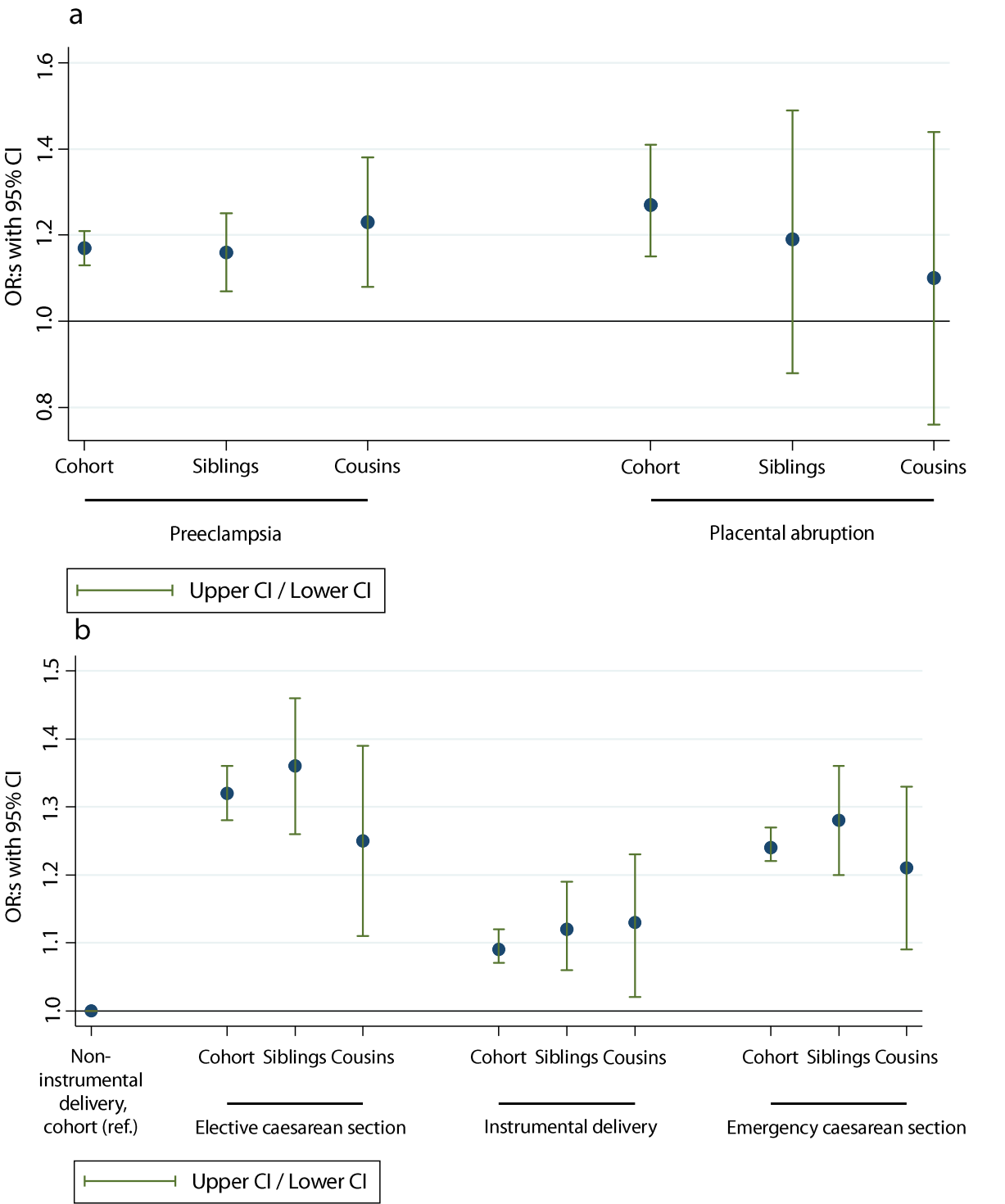


Figure 7a-b. Adjusted* odds ratios and 95% confidence intervals for the association between maternal asthma† and perinatal outcomes in Study I.

*Adjusted for age, BMI, parity, smoking at antenatal care admission, country of birth, cohabitation/marital status, and level of education.

†Asthma recorded in the Swedish Medical Birth Register, asthma diagnosis in the Swedish National Patient Register and/or asthma medication dispensed at least twice according to the Swedish Prescribed Drug Register.

In Study II (n = 1,075,153), we confirmed these associations for the outcomes we studied (preeclampsia – adjusted OR 1.17; 95% CI 1.13-1.21, placental abruption – adjusted OR 1.27; 95% CI 1.15-1.41, instrumental delivery, caesarean section, lower birth weight, lower gestational age and small for gestational age – adjusted OR 1.18; 95% CI 1.12-1.23). In Study II, when adjusting for unmeasured genetic and environmental factors by comparing cousins and siblings discordant for exposure and outcomes, we saw that significant associations remained for preeclampsia, caesarean section, instrumental delivery, lower gestational age, and lower birth weight, Figure 8a-c.



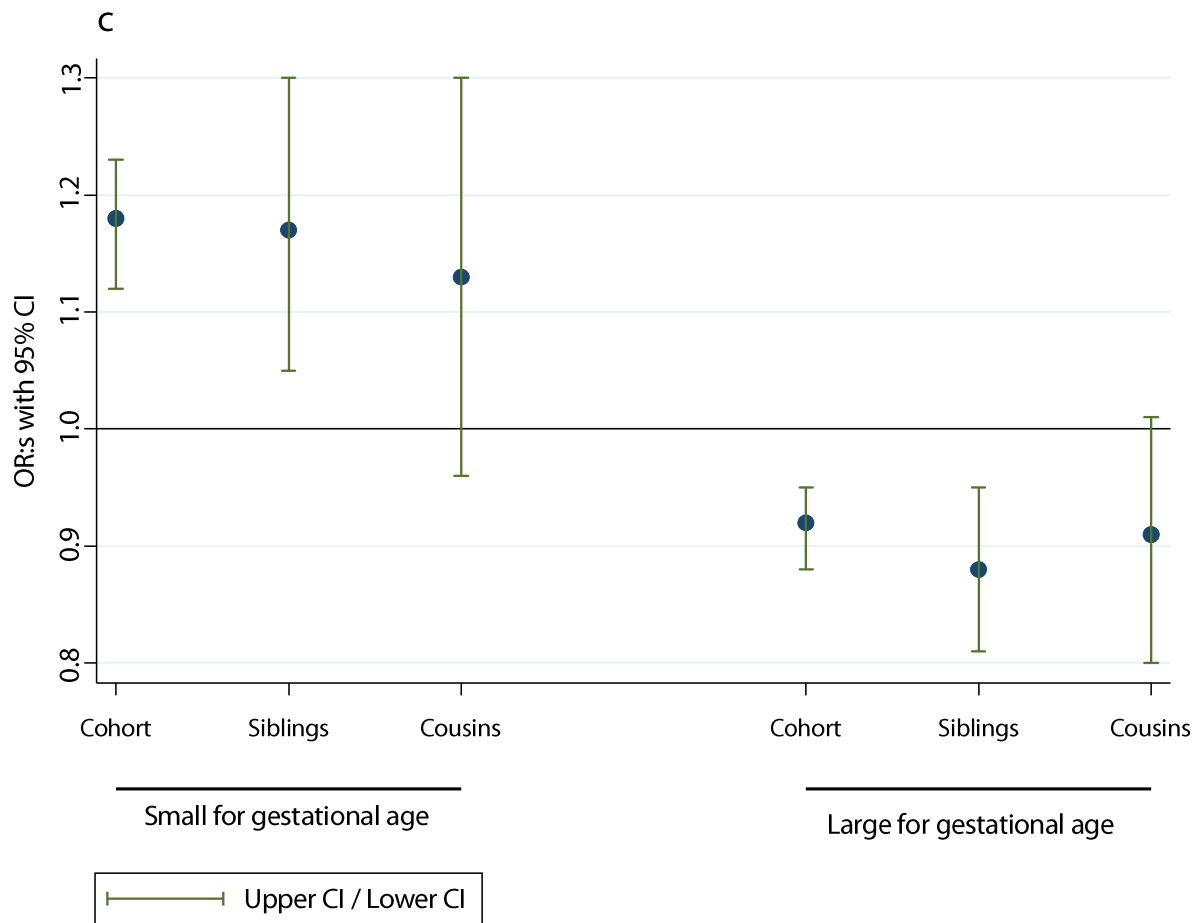
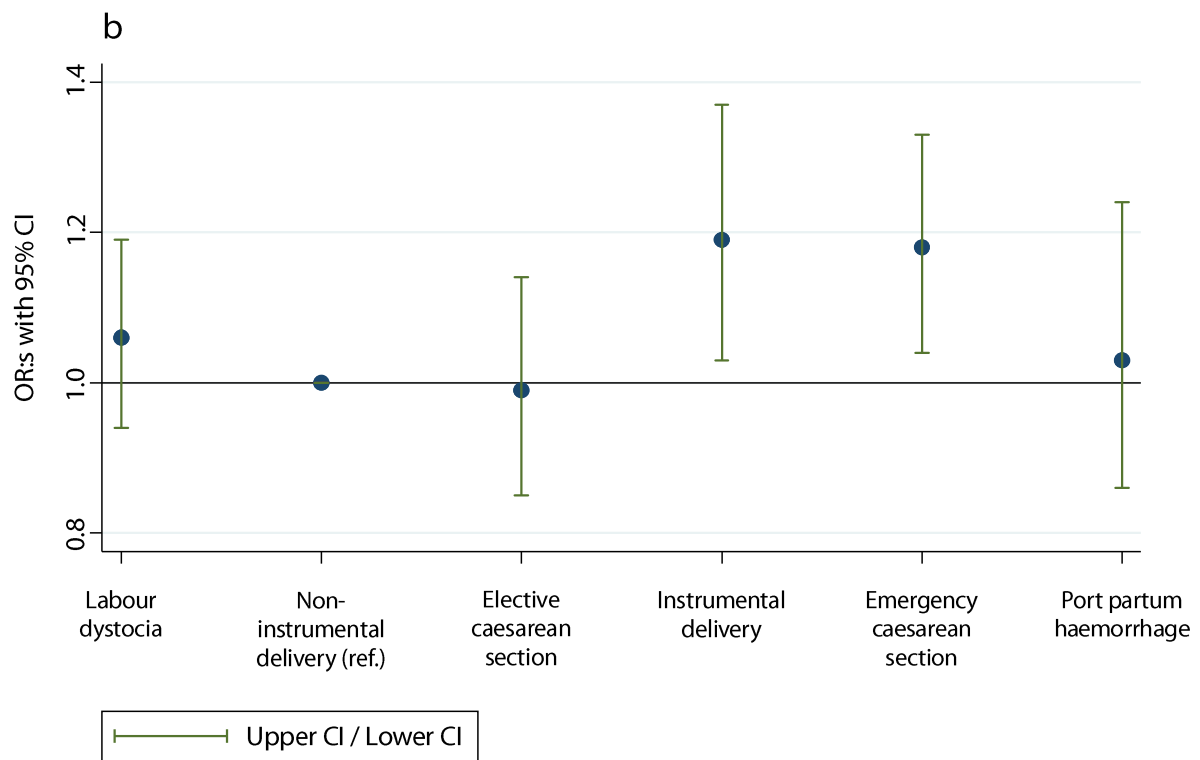
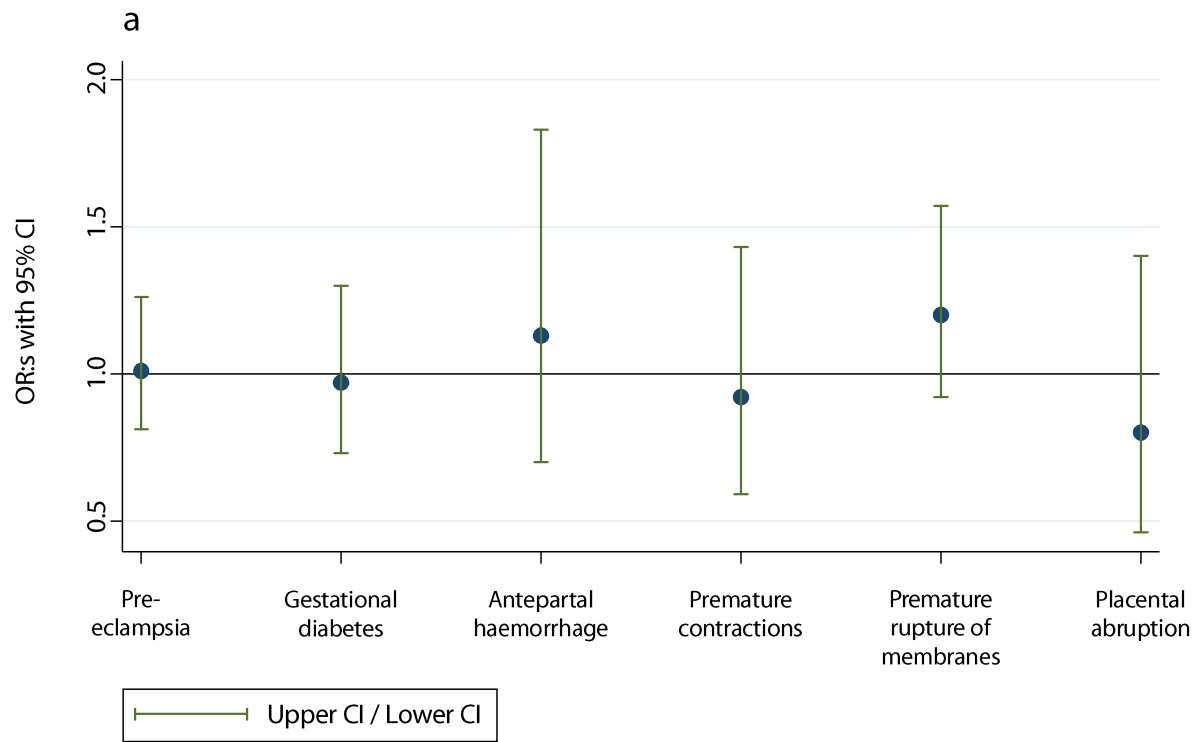


Figure 8a-c. Adjusted* odds ratios with 95% confidence intervals for the associations between maternal asthma† and adverse pregnancy, labour and perinatal outcomes.
 *Adjusted for age, BMI, parity, smoking at antenatal care admission, country of birth, cohabitation/marital status, and level of education
 †Asthma recorded in the Swedish Medical Birth Register, asthma diagnosis in the Swedish National Patient Register, and/or asthma medication dispensed at least twice from the year before pregnancy until delivery according to the Swedish Prescribed Drug Register.

Moreover, in Study I, we saw that the risks of adverse outcomes such as low birth weight increased with increasing asthma severity, Figure 9a-c.



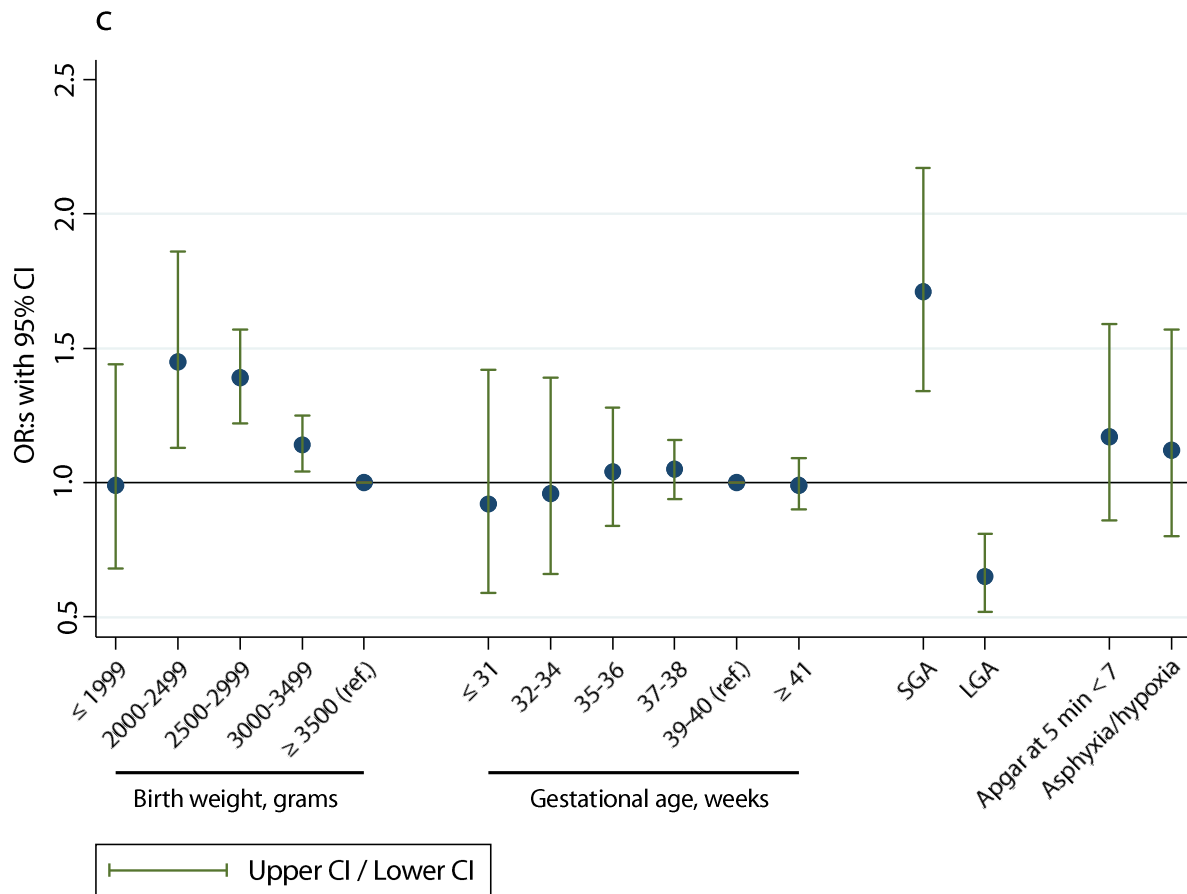
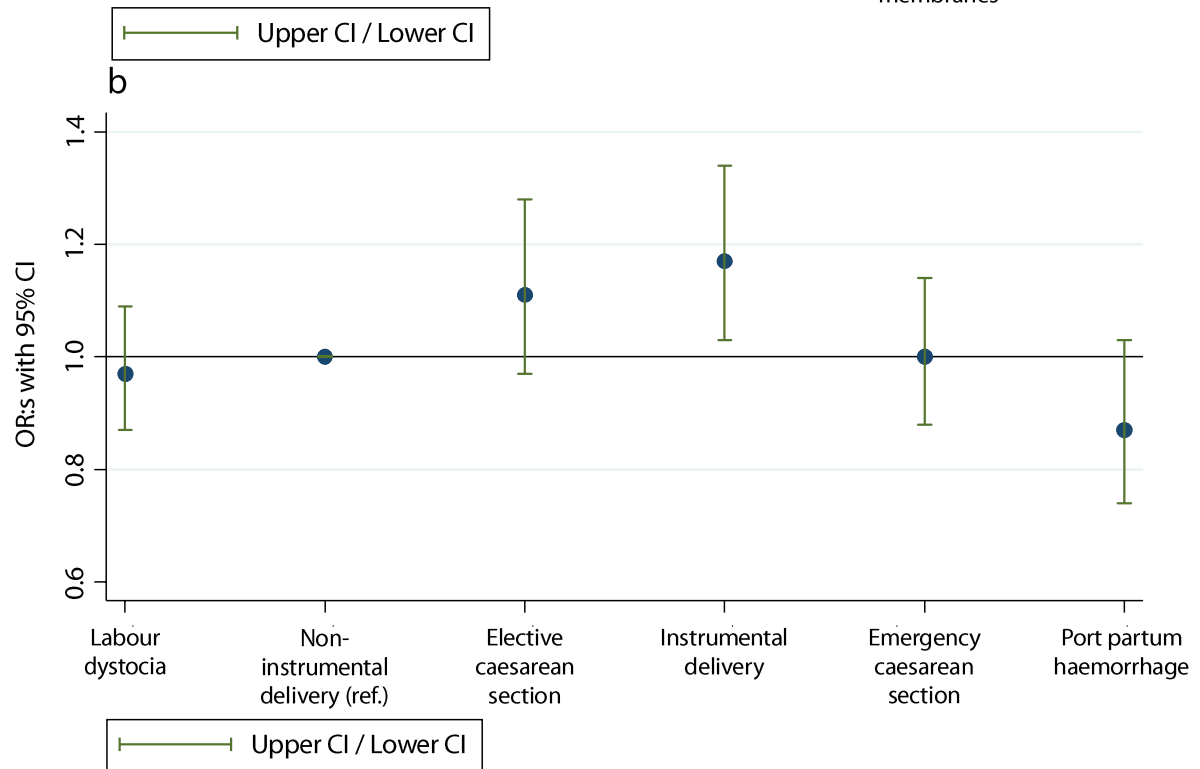
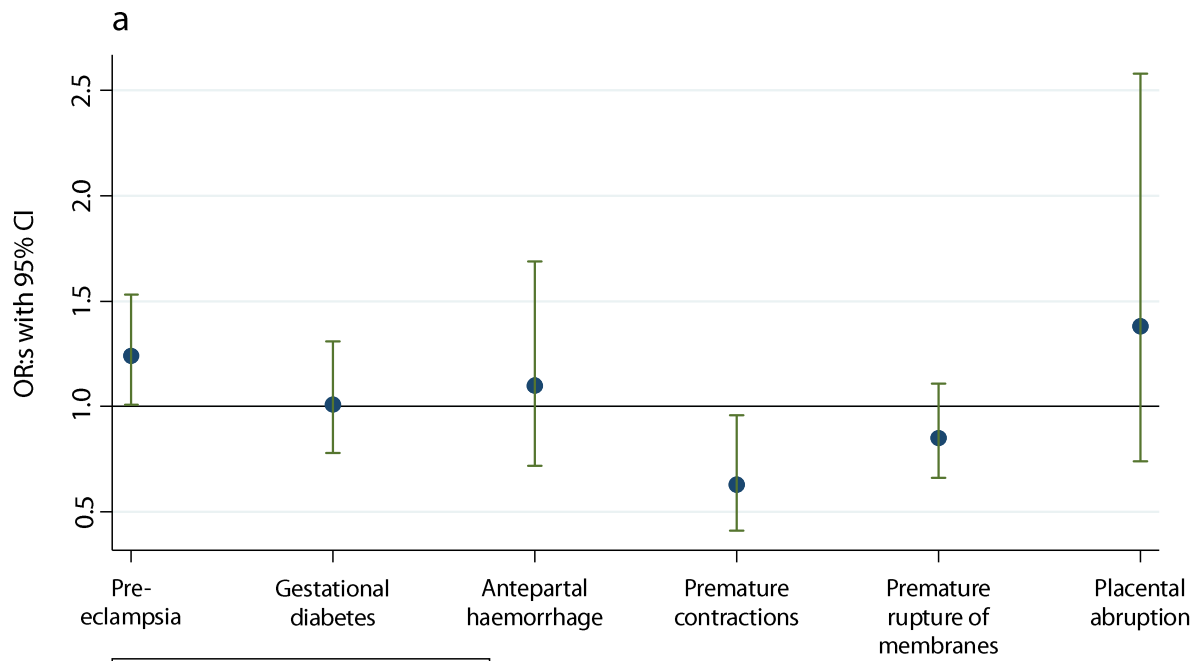


Figure 9a-c. Adjusted* odds ratios with 95 % confidence intervals for the associations between moderate/severe asthma in the year before pregnancy and perinatal outcomes, mild asthma as reference.

*Adjusted for age, BMI, parity, smoking at antenatal care admission, country of birth, cohabitation/marital status, and level of education.

For women with uncontrolled compared to controlled asthma the results for adverse outcomes were inconsistent displaying both increased and decreased odds ratios for different outcomes, Figure 10a-c.



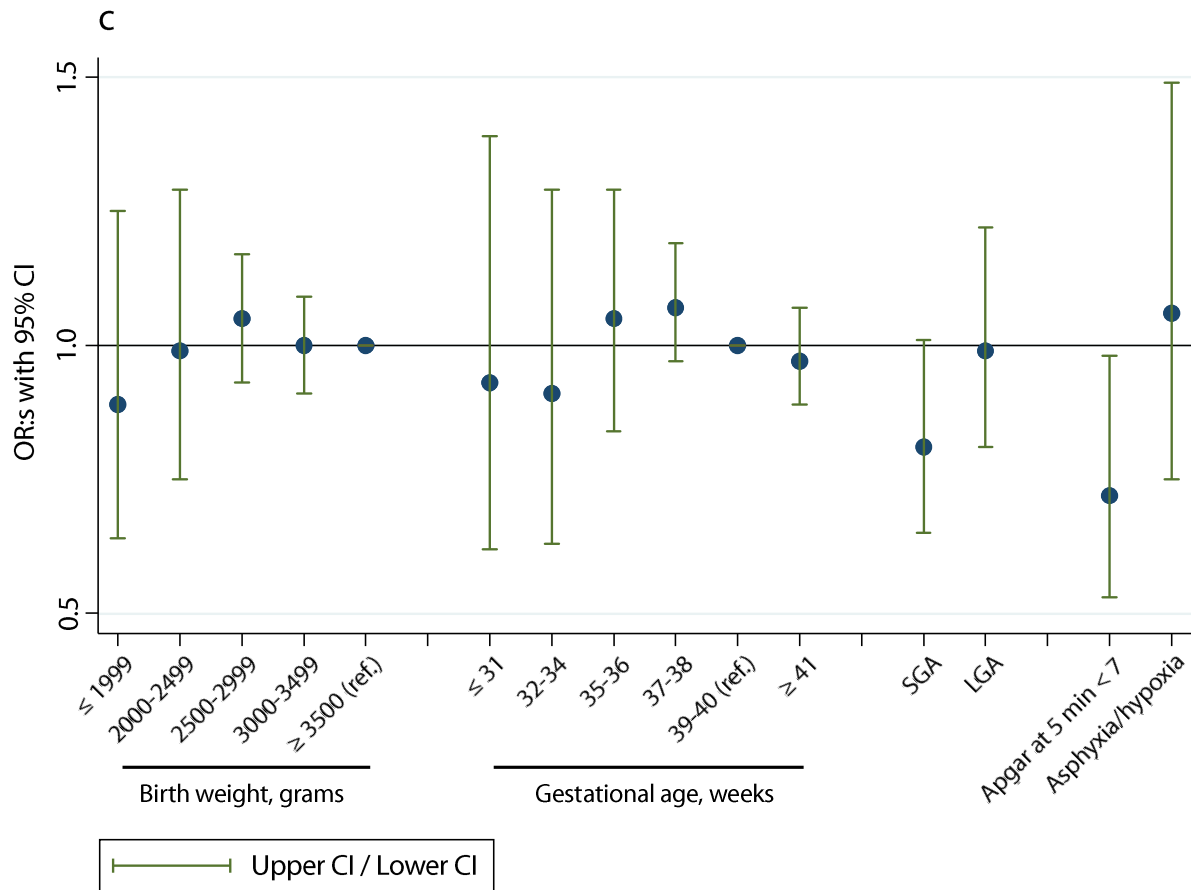


Figure 10a-c. Adjusted* odds ratios with 95% confidence intervals for the associations between perinatal outcomes and asthma control in the year before pregnancy.

*Adjusted for asthma severity, country of birth, smoking at antenatal admission, cohabitation and marital status, maternal education level, BMI, maternal age at delivery.

5.2 STUDY III

In the MAESTRO-cohort (n = 1693), the asthma prevalence in pregnant women was 15%.

Figure 11 shows the distribution of measured discrepancies between first and second trimester. We saw small mean discrepancies in days between estimated and expected gestational age at second trimester among women with (-1.2) and without (-1.1) asthma, and we did not see any significant differences between the groups (adjusted OR 1.57; 95% CI 0.88-2.81 for a negative discrepancy of 6 days or more). Furthermore, we didn't see any significant difference in mean gestational age, birth weight, or length of child.

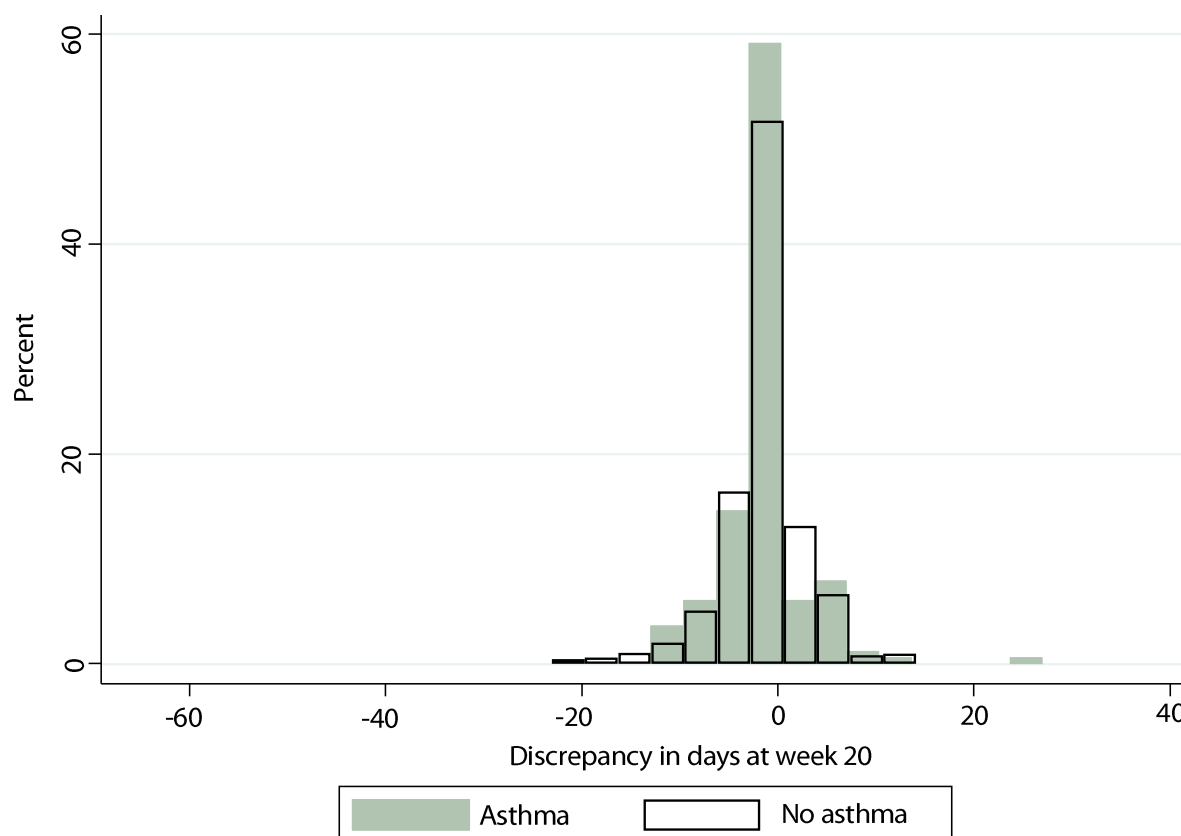


Figure 11. Distribution of measured discrepancy in women with asthma and women without asthma. Discrepancy equals the difference in days between estimated and expected length of pregnancy at second trimester ultrasound scan, around gestational week 20.

When assessing asthma control the mean discrepancy at the second trimester assessment was -2.0 days for women with uncontrolled asthma and -0.9 days for women with controlled asthma, however the differences between the groups again non-significant.

5.3 STUDY IV

In Study IV (n = 950,301), we found a prevalence of 5.9% for women in the cohort having anxiety or depression medication or diagnosis during the year before pregnancy until delivery (current disease). The prevalence of current maternal asthma was 4.0%, and only 0.5% were exposed to both anxiety or depression and asthma. Anxiety or depression was associated with higher odds for preeclampsia/eclampsia, caesarean section, vaginal instrumental delivery, lower mean birth weight, lower mean gestational age and large for gestational age. When comparing cousins and siblings discordant for the exposure and outcomes the point estimates changed very little or not at all, indicating no confounding from factors (genetic or environmental) shared within families, Appendix IV; Table 2 and Table 3.

In the interaction analyses we could see that a combination of anxiety or depression and asthma showed higher odds ratios for most of the outcomes compared to the reference group having neither exposure, Appendix IV; Figure 1. Still we couldn't see any additive interaction

between the two exposures. On the multiplicative scale, only elective caesarean section was affected by interaction between asthma and anxiety or depression. In a sensitivity analysis of women with a diagnosis for anxiety or depression with or without medication there were small differences between the groups, except for the outcome elective caesarean section where women without medication had significantly higher odds ratios for the outcome, Figure 12.

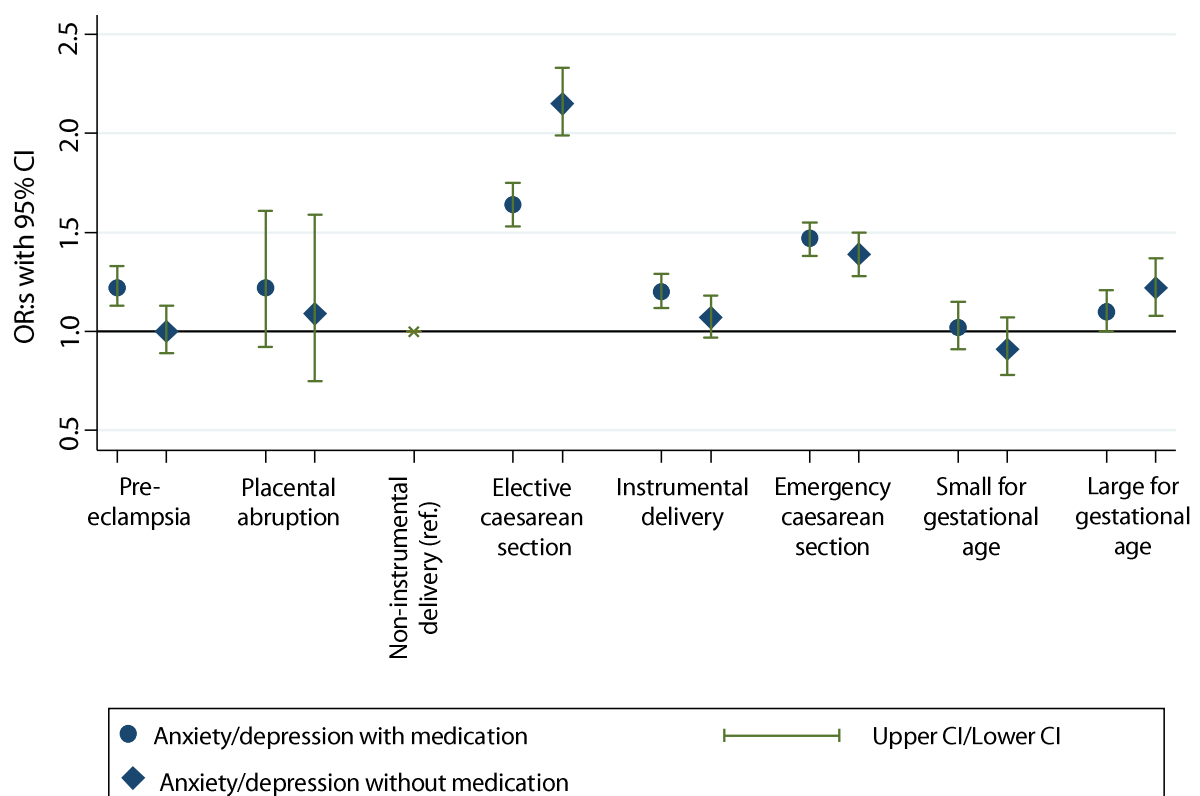


Figure 12. Pregnancies with maternal anxiety/depression diagnose in the year before pregnancy until delivery with or without medication. Years 2006-2013. Adjusted* odds ratios with 95% confidence intervals for the associations between exposures and outcomes.
*Adjusted for country of birth, smoking, cohabitation, maternal education level, BMI, age

5.4 DISCUSSION AND METHODOLOGICAL CONSIDERATIONS

We have been able to show that maternal asthma is associated with several serious pregnancy-, delivery and perinatal outcomes such as preeclampsia emergency caesarean section and small for gestational age. We have also demonstrated that the associations are not confounded by factors shared within families, such as common genes and environment. Indeed, it seems that asthma itself is responsible. We didn't see any difference in early foetal growth in asthmatic mothers compared to pregnant women without asthma. We have also shown that maternal anxiety or depression during pregnancy is associated with many of the same outcomes as asthma, but there are no apparent interactions between the conditions.

5.4.1 Study designs

Study I, II, and IV are all register-based and include data that have been prospectively collected, without any notion of our research questions. This approach has many advantages since it eliminates the risk of many types of bias that can be introduced for instance when setting up a clinical cohort such as selection bias. However, observational studies are prone to confounding and despite the fact that we considered and included possible confounders there are possible factors that are unmeasured that still could affect the estimates. By using relatives that to some extent share genes and environment (for instance siblings and cousins), but are discordant in terms of exposure and outcome, it is possible to account for some of these unmeasured confounding factors. We have been able to do this for Study II and IV and overall the estimates were found to be unchanged, suggesting that both asthma and anxiety or depression are causal in the effect on pregnancy and pregnancy outcomes. There are, however some limitations to this method. By choosing close relatives like siblings that differ in both exposure and outcome, they may be less alike than they would normally be by chance. This means that they will be more biased on non-shared factors than an unpaired estimate. Random measurement errors will also be attenuated in a within-pair-analysis, and since it is difficult to find discordant siblings or cousins, the power will be greatly reduced.^{99, 119} We have tried to get data on exposure from different sources, such as the medical birth register, the national patient register and the prescribed drugs register in order to minimise the impact of measurement error and to increase power.

In Study III we have collected data prospectively in a clinical cohort. Some of the data come from questionnaires in which we asked the participants about background factors and medical conditions. This approach can introduce recall bias and there is also a risk of selection bias in a clinical cohort since participants volunteer to be included and there is no random selection. Participants who are more educated or who have an interest in the disease may be more likely to enrol, and therefore included individuals may differ from the general population in terms of background factors such as education, and health. This is very hard to avoid, and adjusting for selection bias is difficult.¹²⁰ Ways to minimise the introduction of selection bias, attempted in the MAESTRO study, is to recruit at different locations in order to get a more diverse study population, and to make the rationale of a study broader than just looking at one disease therefore appealing to a wider audience.

5.4.2 Internal and external validity

The selection of biased populations is harmful to the internal validity of the studies. Information bias or misclassification can also affect the internal validity and in the studies. For the register-based studies, any misclassification is more likely to be non-differential which means that the magnitude of the associations might be underestimated. The maternal diagnoses in the Medical Birth Register for instance are reliable to large extent. On the other hand, the infant diagnoses, other than, sex, gestational age, and birth weight suffer from low report rates, with missing data on up to 23%.¹⁰⁴ Self-reported asthma and asthma control in Study III may be subject to report bias, with participants answering differently when they

know of the research question. Potential misclassification of exposure and/or outcomes (for instance measurement error by ultrasound scan) is most likely independent of each other, suggesting non-differential misclassification.¹²¹

The external validity and generalisability of a study is dependent on the internal validity – without a good internal validity it's difficult to generalise to other populations.¹²² For Study I, II, and IV we have identified all Swedish women that gave birth during the respective study period. This means that the results should be generalisable to other similar populations with similar characteristics, such as other westernised countries. Study III is smaller and based on pregnant women from a specific region (Stockholm) that attended eight different antenatal clinics. There may be limited generalisability to other populations, although we have strengthened the internal validity by adjusting for known possible confounders.

5.4.3 Interaction analyses

If the effects on the outcome by two exposures put together is different from the combination of the two effects considered separately an interaction is likely to be present. When looking at associations between exposures and outcomes it's important to test for possible interactions, especially from a public health perspective, since it will help determining if two exposures of interest can be studied separately or should be considered together.¹²³ Interaction can, as mentioned above, be tested on both additive and multiplicative scale. Even though multiplicative interaction can aid in determining underlying mechanisms, the magnitude is assessed by looking at additive interaction.¹²⁴ In linear regression, additive interaction is easily calculated. For logistic regression models it is necessary to do additional calculations to determine the magnitude of additive interaction, for instance by the use of RERI (Relative Excess Risk due to Interaction).¹²⁵ One might have assumed that there would be interaction between maternal asthma and anxiety/depression. However, we were unable to confirm this in Study IV, which means that the two exposures indeed can and should be assessed separately.

5.4.4 Assessing early growth retardation

In Study III we assessed maternal asthma as a risk factor for early growth retardation. The rationale for choosing this outcome was that we had seen in Study I and II and in other studies^{40, 126} that maternal asthma is a risk factor for the child being born small for gestational age, and low birth weight. We wanted to know if the growth retardation occurred early or late during pregnancy and by looking at the calculated gestational age at the second trimester routine ultrasound we would be able to determine when the growth retardation occurs. This way of assessing foetal growth comes with some assumptions. First, since we chose an early ultrasound as our reference point we assumed that early growth retardation occurs after the first trimester. There may also be growth restriction in the first trimester, but such an early reduction in foetal growth is associated with increased risk of subsequent miscarriage,¹²⁷⁻¹²⁹ and never reaching 20 weeks of gestation. Second, we also assumed that all pregnancies have similar early growth, regardless of maternal or paternal influences. Indeed, previous studies

show that this is mostly true, with standardised growth curves showing larger variance later in pregnancy.^{92, 96, 130} We therefore believe that, although resting on some assumptions, our method on assessing early foetal growth is valid.

6 ETHICAL CONSIDERATIONS

Ethical consent for the studies has been obtained by the Regional Ethical Review Board in Stockholm; for Study I: 2010/1258-32. For Study II, III and IV: 2011/526-31/2 with amendments 2012/2199-32, 2014/971-32, 2014/2037-32. For Study III also with amendment 2017/1679-32 and for Study IV also with amendment 2013/862-31/5.

This PhD-project includes data collected both from register-based data linkage (Study I, II and IV) and from a clinical cohort (Study III). These have similar and some different ethical considerations.

6.1 RISKS

In register-based studies, although data have been de-identified, the gathered information is still very sensitive and needs to be held in a secure environment with secure servers, strong firewalls and encrypted, password-protected computers. To limit access to the personal data, only database administrators have access to all information stored and any researcher accesses only the re-anonymised linked variables they need. The published data must be presented on a group level (minimum 10 in a group). This means that identification of a single individual should not be possible.

Normally study participants need to be informed of a study, and consent from each individual has to be collected. In a register-based study in Sweden, informed consent is often waived by the ethical review board. Also, studying common exposures and outcomes, such as asthma and pregnancy outcomes minimizes the risk of subgrouping to a level that would allow the identification of individuals and intruding on the personal integrity.

For a study like the clinical Study III the approach was to obtain informed consent from each participant after careful and detailed information was provided to the participant about the study setup, including collection, storage, and security of data. The participants were also informed that they could at any given time and without any special reason withdraw from the study and, if they wanted, have their gathered data disposed of. To minimize the risk of intruding personal integrity, personnel performing tasks like bio sampling or lung function measurements were unaware of, for example, how the study person answered in the questionnaires and other aspects of the study. At time of analysis, all information on study persons was de-identified.

If interventions in a clinical study are part of routine health care, e.g. spirometry, no apparent associated risks are normally present. If interventions are not within the scope of routine health care, further considerations regarding risks and benefits must be taken.

6.2 BENEFITS

For register-based studies, there are no immediate individual benefits for a study participant. In a clinical study (like our Study III) there are possible benefits on an individual level since, for example, a participant can get access to important health parameters concerning her health

status and thereby can get information on whether she needs to for instance alter her medication.

For all studies there are possible benefits on a population level, meaning that the results can help the understanding and course of a disease and maybe how to better control it. In that sense there are many more individuals with a potential benefit than only those participating in a study.

6.3 ETHICAL CONCLUSION

In conclusion, there are some risks with all studies. But with a good research question and having strict rules set up for collecting samples, analysing and storing of data and presentation of results, the potential benefits to the society that this particular research adds outweigh the risks.

7 INTERPRETATION AND CONCLUSION

Maternal asthma is associated with a number of serious pregnancy complications and adverse perinatal outcomes (Study I and II). Some complications are more frequent with increased asthma severity (Study I). Maternal asthma seems not to be associated with early foetal growth restriction (Study III). Maternal anxiety or depression during pregnancy is also associated with adverse outcomes in pregnancy, and although showing similarities with maternal asthma during pregnancy, we could not detect significant interactions between the conditions (Study IV).

After adjusting for familial confounding conditioning on siblings and cousins, asthma as well as anxiety or depression remains significantly associated with adverse pregnancy outcomes (Study II and IV).

Targeting the asthma disease and anxiety or depression in the pregnant mother will continue to be important in reducing risks for adverse outcomes in pregnancy. With greater awareness and proper management, outcomes would most likely improve.

8 FUTURE PERSPECTIVES

Asthma burdens pregnancies, affecting both mother and offspring, as we have seen in the studies covered in this thesis. Ideally, we would be able to prevent adverse events by identifying early those women affected and managing their disease in an optimal way. This could be achieved by setting up specific antenatal clinics for women with asthma, similar to those for women with diabetes during pregnancy.^{131, 132}

We have seen that although there are some differences in how asthma severity and control affect our studied outcomes, asthma poses risks regardless of the level severity or control. One of the major difficulties is to determine which women would benefit the most from more intense interventions. Perhaps asthmatic women with an allergic phenotype are the ones with the highest risk of adverse events, as this is considered one of the driving pathways towards more severe disease.^{8, 133}

Future research on maternal asthma should look more into the possibilities of determining asthma phenotypes – by assessing genetic traits, allergies, and lung function measurements – and how they affect pregnancy outcomes, with much of this data is already collected within the scope of the MAESTRO study. In order to determine when foetal growth retardation in asthmatic women occurs during pregnancy, larger studies with more ultrasound measurement data are needed. Large cohorts looking at seasonal differences could also help assess if foetal growth retardation in asthmatic women is more likely if pollen season occurs during the first, second or third trimester of pregnancy.

Intervention studies on maternal asthma, perhaps in a specialised antenatal clinic setting, could help improve outcomes in women affected. Intervention should focus treating those with the worst expected outcomes. One way of doing this is by monitoring the fraction of exhaled nitric oxide (FeNO) levels for early intervention to limit the inflammatory process, something that has been studied previously^{134, 135} but outcomes can be expanded to include more maternal complications such as preeclampsia.

Women with internalising disorders such as stress, anxiety or depression have not only higher risks for post-partum depression but also for adverse outcomes in pregnancy as we have been able to show in Study IV. Among other things we could see that women with diagnosis of anxiety or depression had higher odds for elective caesarean section if they were not on medication. While several of the outcomes studied may be difficult to prevent, elective caesarean section is associated with severe morbidity and often preventable.^{136, 137} Greater awareness of our found associations in maternal and obstetric health care is necessary. Based on Study IV data it's difficult to determine why some of the women with anxiety or depression diagnosis were not using medication. Future studies on stress, anxiety or depression during pregnancy should focus on optimising treatment and reducing rates of caesarean section by an early intervention. Closer monitoring of women with anxiety or depression in specialised antenatal clinics (clinics that are many times implemented already) is vital for such an early intervention.

9 SVENSK SAMMANFATTNING

Astma liksom ångest och depression är associerade med komplikationer under graviditet och förlossning. Det finns också samband mellan ångest/depression och astma och det kan finnas gemensamma mekanismer bakom hur dessa åkommor påverkar graviditet och graviditetsutfall. Till exempel skulle en del av associationerna kunna förklaras av genetiska faktorer eller miljöfaktorer, faktorer som delas inom familjer. I denna avhandling har vi studerat hur astma och ångest eller depression påverkar graviditet och förlossning i en kombination av stora populationsbaserade studier och en mindre klinisk kohort. Med hjälp av familjedesign som statistisk metod har vi tagit hänsyn till genetiska faktorer och delad miljö.

I **Studie I och II** har vi i nationella studiepopulationer tittat på sambandet mellan moderns astma och graviditets- och förlossningsutfall såsom havandeskapsförgiftning, moderkaksavlossning, förlossningssätt, födelsevikt och graviditetslängd vid födseln. I **Studie II** identifierade vi kusiner och systrar som var gravida och födde barn under samma studieperiod. Vi fann samband mellan moderns astma och många av de studerade utfallen, tex havandeskapsförgiftning (**Studie I och II**) och sambanden kunde inte förklaras av andra faktorer (genetik eller miljö) inom familjer (**Studie II**). Vi såg också ökad risk för vissa av utfallen vid svårare eller sämre kontrollerad astma (**Studie I**).

I **Studie III** undersökte vi hur moderns astma påverkade tidig fetal tillväxt genom att använda oss av data från rutinultraljudet i andra trimestern. Studiepopulationen vi använde oss av var MAESTRO-studien där 1693 kvinnor följdes under graviditeten. Vi kunde inte se någon signifikant skillnad mellan kvinnor med och utan astma och tidig fetal tillväxt. Vi kunde inte heller se någon skillnad mellan grupperna när vi tittade på födelsevikt och graviditetslängd vid födseln.

I **Studie IV** undersökte vi, med hjälp av en nationell studiepopulation, sambandet mellan ångest eller depression hos den gravida kvinnan och avvikande graviditets- och förlossningsutfall. Vi fann samband mellan ångest eller depression hos modern och flera avvikande utfall och att sambanden inte kunde förklaras av faktorer som delades inom familjer (mellan kusiner eller systrar). Vi såg inte heller någon interaktion mellan ångest eller depression och astma för något utfall, förutom vid planerat kejsarsnitt. Vi såg också högre oddskvoter för planerat kejsarsnitt hos kvinnor med ångest eller depressionsdiagnos *utan* medicinering jämfört med kvinnor som medicinerade.

Sammanfattningsvis har vi kunnat visa att astma liksom ångest eller depression är associerade med allvarliga graviditets- och förlossningskomplikationer. Genetiska faktorer eller miljöfaktorer som delas av familjer kan inte förklara sambanden. Förutom vid planerat kejsarsnitt kunde vi inte se någon interaktion mellan ångest eller depression och astma under graviditeten vid de studerade utfallen. Det betyder att både ångest eller depression och astma hos den gravida kvinnan fortsätter vara viktiga mål för att minska risken för graviditets- och förlossningskomplikationer. Större medvetenhet och optimal behandling förbättrar sannolikt utfallen för både kvinnan och barnet.

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